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HISTOPLASMOSIS

Cutaneous and Mucomembranous Lesions, Mycologic and Pathologic Observations

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HISTOPLASMOSIS should be of interest to dermatologists because cutaneous or mucomembranous lesions have been observed in one half of the reported cases. The literature has been reviewed, disclosing reports on 88 patients with the disease. In 1945, Parsons and Zarafonetis [1] referred to 71 of these cases. We have read of 17 more [2]

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1. Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man: Report of Seven Cases and a Review of Seventy-One Cases, Arch. Int Med. **75**:1 (Jan.) 1945.

2. (*a*) Strong, R. P.: A Study of Some Tropical Ulcerations of the Skin with Particular Reference to Their Etiology, Philippine J. Sc. **1**:91 (Jan.) 1906. (*b*) Alonso, J. M., and Cancelo Freijo, J.: Histoplasmosis of Darling: First Observations of a Patient in Uruguay; Clinical Cure with Sulfadiazine, Arch. urug. de med., cir. y especialid. **24**:193 (March) 1944. (*c*) Balina, P.; Herrera, J. A.; Bosq, P., and Negroni, P.: Tercer caso Argentino de histoplasmosis: Beneficio de la sulfamidoterapia, Rev. argent. dermatosif. **27**:453 (Sept.) 1943. (*d*) Boltjes, B.: Histoplasmosis: Report of a Case with Brief Review of the Literature, J. Kansas M. Soc. **44**:226 (July) 1943. (*e*) Christie, A., and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health **35**:1131 (Nov.) 1945. (*f*) German, W. M.; Ashmun, S., and Dille, C. E.: Histoplasmosis: Case Report, Am. J. Clin. Path. **13**:12 (Jan.) 1943. (*g*) Kemper, J. W., and Bloom, H. J.: Histoplasmosis: Report of a Case, J. Oral Surg. **2**:167 (April) 1944. (*h*) Martin, W. P., and Silber, B.: Histoplasmosis of Darling (Reticuloendothelial Cytomycosis): Case Report, Am. J. Clin. Path. **14**:119 (Feb.) 1944. (*i*) McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplas-

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and have added 1 of our own. Cutaneous or mucomembranous lesions were observed in 45 (50 per cent) of the 88 patients.[3] We believe that these facts warrant a review of the subject.

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mosis: A Report of Four Cases, Two in Siblings; Histoplasmin Test and Other Diagnostic Procedures, J. Pediat. **28**:275 (March) 1946. (*j*) Moore, M., and Jorstad, L. H.: Histoplasmosis and Its Importance to Otorhinolaryngologists: A Review with Report of a New Case, Ann. Otol., Rhin. & Laryng. **52**: 779 (Dec.) 1943. (*k*) Schultze, cited by Ciferri, R.; Redaelli, P., and Visocchi, V.: The Histoplasmoceae Family, Mycopathologia **1**:104, 1938. (*l*) Schlumberger, H. G., and Service, A. C.: A Case of Histoplasmosis in an Infant with Autopsy, Am. J. M. Sc. **207**:230 (Feb.) 1944. (*m*) Wohlwill, F., and Morais, D.: Histoplasmose de Darling (1 caso observado em Portugal), Lisboa méd. **20**:403, 1943. (*n*) Woodruff, E., and Castellanos, L.: Histoplasmosis, Rev. mex. de tuberc. **7**:215 (July-Aug.) 1945. (*o*) Worgan, D. K.: Histoplasmosis: A Summary of the Known Facts About the Disease; Report of a Case, Bull. School Med. Univ. Maryland **30**:69 (Oct.) 1945. (*p*) Perrin, T. G.: Nota sobre el primer caso de histoplasmosis en México, Rev. d. Inst. salub. y enferm. trop. **4**:79 (March) 1943. (*q*) Iams, A.; Tenen, M. M., and Flanagan, H. F.: Histoplasmosis in Children: Review of the Literature, with Report of a Case, Am. J. Dis. Child. **70**:229 (Oct.) 1945.

3. (*a*) Strong.[2a] (*b*) Alonso and Cancelo Feijo.[2b] (*c*) Balina, Herrera, Bosq and Negroni.[2c] (*d*) Kemper and Bloom.[2g] (*e*) Worgan.[2o] (*f*) Perrin.[2p] (*g*) Iams, Tenen and Flanagan.[2q] (*h*) Darling, T.: A Protozoon General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen, and Lymph Nodes, J. A. M. A. **46**:1283 (April 28) 1906; (*i*) Histoplasmosis: A Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America, Arch. Int. Med. **2**:107 (Sept.) 1908. (*j*) Riehl, G.: Durch pathogene Sprosspilze bedingte Granuloma, Arch. f. Dermat. u. Syph. **148**:392, 1925. (*k*) Shaffer, F. J.; Shaul, J. F., and Mitchell, R. H.: Histoplasmosis of Darling, J. A. M. A. **113**:484 (Aug. 5) 1939. (*l*) Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man Caused by a New Yeast-like Organism, a Pathogenic Member of the Genus Sepedonium, Am. J. Path. **10**:731 (Nov.) 1934. (*m*) Gunter, W. A., and Lafferty, C.: Histoplasmosis of Darling, J. M. A. Alabama **9**:337 (April) 1940. (*n*) Clemens, H. H., and Barnes, M. L.: Histoplasmosis of Darling, South. M. J. **33**:11 (Jan.) 1940. (*o*) Wade, H. W., cited by Meleney.[3h'] (*p*) Humphrey, A. A.: Reticuloendothelial Cytomycosis (Histoplasmosis of Darling), Arch. Int. Med. **65**:902 (May) 1940. (*q*) Balina, P. L.; Negroni, P.; Bosq, P., and Herrera, J. A.: Histoplasmosis de Darling, Rev. argent. dermatosif. **25**:491, 1941. (*r*) Anderson, W. A. D.; Michelson, I. D., and Dunn, T. M.: Histoplasmosis in Infancy, Am. J. Clin. Path. **11**:344 (April) 1941. (*s*) Villela, E., and Madureira, P.: Histoplasmose em crianca no estado de Minas Geraes, Rev. brasil. de biol. **1**:449 (Dec.) 1941. (*t*) de Almeida, F., and da Silva Lacaz, C.: Cogumelo de genero *Histoplasma* isolado de lesoes de cromomicose: Associacao de fungos nos lesoes, Folia clin. et biol. **11**:65, 1939. (*u*) Derry, D. C. L.; Card, W. I.; Wilson, R., and Duncan, J. T.: Histoplasmosis of Darling: Report of Case; Mycological Notes, Lancet **1**:224 (Feb. 21) 1942. (*v*) Palmer, A. E.; Amolsch, A. L., and Shaffer, L. W.: Histoplasmosis with Mucocutaneous Manifestations, Arch. Dermat. & Syph. **45**:912 (May) 1942. (*w*) Dean, L. W., Jr.: Histoplasmosis of the Larynx, Arch. Otolaryng. **36**:390 (Sept.) 1942. (*x*) Thomas, W. C., and Morehead, R. P.: Histoplasmosis, North Carolina M. J.

HISTORICAL REVIEW

Darling observed the first cases of histoplasmosis in Panama in 1906,[3h] 1908 [3i] and 1909 [4] while searching for examples of visceral and cutaneous leishmaniasis. Strong [2a] saw a patient in the Philippine Islands at about the same time with an abscess which may have been due to the same or to a similar organism. Darling named the causative agent Histoplasma capsulatum and stated the belief that it was a protozoon, because of its similarity to the organism causing kala-azar. DeMonbreun [5] in 1934 furnished definite proof that the organism is a fungus. Its habitat in nature, modes of transmission and portal of entry into the human body have as yet not been determined. No new cases of histoplasmosis were recognized from 1909 until 1926, when 2 were reported. Since then the disease has been observed with increasing frequency.

EPIDEMIOLOGY

The sources of infection and the modes of transmission of H. capsulatum, as already stated, have not as yet been elucidated. We are

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4:378 (Sept.) 1943. (*y*) Beamer, P. R.; Smith, E. R., and Barnett, H. L.: Histoplasmosis, J. Pediat. **24**:270 (March) 1944. (*z*) Negroni, P.: Estudio micológico del primer caso sud-americano de histoplasmosis, Argent. Inst. Bact. **9**:239, 1939-1940. (*a'*) Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man with a New Yeast-like Organism, Am. J. Path. **9**:925 (Nov.) 1935. (*b'*) Parsons, cited by Parsons and Zarafonetis.[1] (*c'*) Steiner, P., cited by Parsons and Zarafonetis (case G).[1] (*d'*) Stingily, cited by Parsons and Zarafonetis (case H).[1] (*e'*) Agress, H., and Gray, S. H.: Histoplasmosis and Reticuloendothelial Hyperplasia, Am. J. Dis. Child. **57**:573 (March) 1939. (*f'*) Brown, A. E.; Havens, F. Z., and Magath, T. B.: Histoplasmosis: Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:812 (Dec. 18) 1940. (*g'*) Henderson, R. C.; Pinkerton, H., and Moore, L. T.: Histoplasma Capsulatum as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. **118**:885 (March 14) 1942 (*h'*) Meleney, H. E.: Histoplasmosis (Reticulo-Endothelial Cytomycosis): A Review with Mention of Thirteen Unpublished Cases, Am. J. Trop. Med. **20**:603 (July) 1940. (*i'*) Simson, F. W., and Barnetson, J.: Histoplasmosis: Report of a Case, J. Path. & Bact. **54**:299 (July) 1942. (*j'*) Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, J. A. M. A. **117**:436 (Aug. 9) 1941. (*k'*) Williams, R. H., and Cromartie, W. J.: Histoplasmosis: Report of a Case, Ann. Int. Med. **13**:2166 (May) 1940. (*l'*) Rhodes, P. H.; Conant, N. F., and Glesne, L. R. B.: Histoplasmosis: Report of a Case in Three Months Old Infant, J. Pediat. **18**:235 (Feb.) 1941. (*m'*) Moore, M., and Blache, J. O., cited by Meleney.[3h'] (*n'*) Hild, J. R.: Histoplasmosis in Infancy, Am. J. Dis. Child. **63**:131 (Jan.) 1942. (*o'*) Mantell, F. J.; Troy, T. S., and Kendall, W. S., cited by Meleney.[3h']

4. Darling, S. T.: The Morphology of the Parasite (Histoplasma Capsulatum) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. **11**:515, 1909.

5. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93 (March) 1934.

familiar only with the parasitic phase of the fungus in man and lower animals, with little evidence available to indicate that the organism leads a saprophytic existence outside the animal body. H. capsulatum may be strictly a parasite, with survival of the fungus depending on transmission from one animal host to another, or it may exist primarily as a saprophyte in nature, only on occasion assuming a parasitic role. Although organisms resembling this fungus have been observed in the tissues of mice [6] and the ferret,[7] the dog is the only animal from which H. capsulatum has been isolated and specifically identified on the basis of cultural characteristics.[8] From available observations it is difficult to assay the role of animals with respect to man's acquisition of the disease, but the dog as a domestic pet in all probability could serve as a reservoir for the infection. Since H. capsulatum may readily be identified in and cultured from the peripheral blood, arthropodan transmission from host to host is not beyond the realm of possibility. The occurrence of 2 cases in siblings reported by McLeod and his associates [21] may be an example of transmission from one brother to the other. Clinical observations of human infections as well as information obtained from experimentally induced infections in laboratory animals indicate that the fungus gains entrance to the body by various routes. Although the pathways of infection followed by H. capsulatum have not as yet been clearly traced, the occurrence of localized oral, cutaneous and nasopharyngeal lesions suggests that these sites of involvement may serve as portals of entry. The factors which govern localization in one patient and widespread dissemination in another are not known. It is becoming evident, as more cases are reported from widely separated areas throughout the world, that histoplasmosis has no geographic limitation. The disease occurs in North, Central and South America, Africa, Europe and in some of the islands in the Pacific Ocean. It is impossible to conclude from the examination of the histories of the comparatively small number of cases of histoplasmosis reported in the literature that the disease has any well defined predilection for age, sex, race or occupation.

With the possible exception of a few instances, infections with H. capsulatum have been of a generalized malignant type with fatal termination. The question as to the probable occurrence of nonapparent and

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6. Sangiorgi, G.: Blastomicosi spontanea nei muridi, Pathologica **14**:493, 1922. Shortt, H. E.: The Pathogenicity of Insect Flagellates to Vertebrates with Special Reference to Herpetomonas Ctenocephali, Fantham, Indian J. M. Research **10**:908 (April) 1923.

7. Levine, N. D.; Dunlap, F. L., and Graham, R.: An Intracellular Parasite Encountered in Ferret, Cornell Vet. **28**:249, 1938.

8. DeMonbreun, W. A.: The Dog as a Natural Host for Histoplasma Capsulatum: Case of Histoplasmosis in This Animal, Am. J. Trop. Med. **19**:565 (Nov.) 1939.

benign forms of the disease has been the subject of considerable speculation recently on the part of several investigators. That histoplasmosis might be the cause of pulmonary calcifications in persons with negative tuberculin reactions was first suggested by Smith [9] in 1943. Christie and Peterson [2e] discussed controversial questions on the relationship of histoplasmosis to the occurrence of pulmonary calcification in those with negative reactions to tuberculin. They exhaustively summarized the observations of previous investigators, which, amplified by their own, clearly indicate ". . . with monotonous regularity the fact that there is in certain sections of the United States a prevalence of pulmonary calcification far beyond what can be explained on the basis of tuberculosis as revealed by tuberculin testing." Christie and Peterson were the first to employ histoplasmin in an intradermal sensitivity test in an appreciable number of patients. During the progress of their studies they tested 181 Tennessee children and observed that 73.5 per cent reacted to histoplasmin. Many of the children who showed a positive reaction had pulmonary calcification and negative reactions to tuberculin. Palmer,[10] following the suggestion of Christie and Peterson, included histoplasmin tests in addition to tuberculin tests and roentgenograms of the chest in his nationwide study of early tuberculosis in student nurses. Of 3,105 nurses studied in Detroit, Kansas City (Missouri and Kansas), Minneapolis and Philadelphia, 22.9 per cent showed definite positive reactions to histoplasmin. The percentage of positive reactions varied considerably in the different cities. Palmer reported that of the nurses reacting only to tuberculin, 10.4 per cent showed calcifications, while of those reacting to histoplasmin, 31.1 per cent showed this process. In the group in which the reactions to both tuberculin and histoplasmin tests were positive, 34.1 per cent showed calcifications. In the large group of 2,141 nurses in which no reactions to either of the antigens occurred, only 1.2 per cent showed pulmonary calcification. In a more recent paper, Palmer [10b] reported on the geographic distribution of sensitivity to histoplasmin in the United States. A group of 8,141 nurses with lifetime residences representing every state and the District of Columbia were tested, and 20.9 per cent of this widespread group reacted to histoplasmin. The region in which the highest percentage of positive reactors occurred includes Tennessee, Kentucky, Arkansas, Missouri, Indiana and parts of Ohio, Illinois, Kansas and Louisiana. This extensive survey of sensitivity to histoplasmin conducted by Palmer shows that the incidence of positive

9. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**:790 (May) 1943.

10. (*a*) Palmer, C. E.: Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, Pub. Health Rep. **60**:513 (May 11) 1945; (*b*) Geographic Differences in Sensitivity to Histoplasmin Among Student Nurses, ibid. **61**:475, 1946.

reactors decreases in proportion to the increasing distance away from the area of high prevalence. It is apparent from his results that geography plays an important role with respect to the prevalence of sensitivity to histoplasmin. The observations and studies of the foregoing investigators indicate that there is a possibility that infection with H. capsulatum is in some way related to the problem of pulmonary calcification in persons with a negative reaction to tuberculin.

One of the most complicated phases of the whole problem is the question of the specificity of histoplasmin. Emmons, Olson and Eldridge [11] clearly demonstrated that cross reactions occur in tests with histoplasmin, blastomycin, coccidioidin and haplosporangin. Guinea pigs infected with H. capsulatum, Blastomyces dermatitidis, Coccidioides immitis and Haplosporangium parvum all showed positive reactions when tested with histoplasmin. The investigators also tested a group of 136 hospital patients with histoplasmin, blastomycin and coccidioidin. Of these, 40.4 per cent reacted to histoplasmin, 25.7 per cent to blastomycin, 3.7 per cent to coccidioidin and 25 per cent to both histoplasmin and blastomycin. The 5 patients who reacted to coccidioidin also showed positive reactions in tests with histoplasmin and blastomycin. Emmons and Ashburn [12] previously had presented evidence, on the basis of infections in animals, that cross sensitivity exists between haplosporangin and coccidioidin. Smith, in a personal communication with Christie and Peterson,[2e] reported that Air Force personnel infected with C. immitis in San Joaquin Valley, Calif., reacted slightly to haplosporangin and more strongly to coccidioidin. However, when men who came to California from Tennessee and Missouri were tested, it was observed that they reacted more strongly to haplosporangin than to coccidioidin.

It is obvious from the observations and studies which have been made that more evidence will have to be presented before it can be definitely established that an infection with H. capsulatum ultimately leads to pulmonary calcification or that sensitivity to histoplasmin is associated with calcification in those with a negative reaction to tuberculin. In view of the frequently noted tendency of fungi to produce cross sensitivity reactions some organism other than H. capsulatum may be the cause of pulmonary calcification. If H. capsulatum is truly the causative agent involved, the ultimate solution of the problem rests on the isolation of the fungus from persons with a benign form of the disease.

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11. Emmons, C. W.; Olson, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease: I. Cross Reactions of Histoplasmin, Pub. Health Rep. **60**:1383 (Nov. 23) 1945.

12. Emmons, C. W., and Ashburn, L. L.: The Isolation of Haplosporangium Parvum N. Sp. and Coccidioides Immitis from Wild Rodents: Their Relationship to Coccidioidomycosis, Pub. Health Rep. **57**:1715 (Nov. 13) 1942.

CLINICAL DIAGNOSIS

It is not possible to make a positive clinical diagnosis of histoplasmosis. It should be considered in infants and adults with various obscure symptoms. While anemia, enlargement of the liver, spleen and lymph nodes, leukopenia, emaciation and fever are usually observed, there may be considerable variation in the clinical observations. The disease may be of long or short duration and may mimic many other conditions.

The cutaneous and mucus membranous lesions of histoplasmosis may resemble closely the involvement seen in tuberculosis, syphilis and deep mycoses. The signs and symptoms observed in lymphoblastomas, especially Hodgkin's disease, leukemia and lymphosarcoma, may be simulated by histoplasmosis. It must be distinguished from kala-azar, malaria, dysentery, typhoid, paratyphoid and neoplasm. The impetiginized, furunculoid and crusted lesions seen in histoplasmosis must be differentiated from impetigo, ecthyma and pyoderma in general. Lack of knowledge of the disease is the main cause of failure in making a diagnosis.

SYSTEMIC MANIFESTATIONS

The clinical picture of histoplasmosis is a variable one. The patients usually have a septic temperature, anemia and leukopenia. In many instances the lymph nodes are enlarged, suggesting Hodgkin's disease or one of the other lymphoblastomas. Pulmonary or adrenal involvement may be a prominent feature, and terminally active tuberculosis may be coexistent. Endocarditis, ulcerative enteritis and involvement of joints due to histoplasmosis have been reported. Occasionally a patient is observed with a localized lesion of recent development which may have resulted from a new infection or may represent renewed activity of a benign and quiescent form of the disease acquired in childhood. In most instances, the infection is progressive and disseminated in character. The systemic manifestations are described in detail by Meleny,[3b] Parsons and Zarafonetis [1] and other authors and will not be discussed further in this paper.

Cutaneous or mucomembranous lesions are observed in many patients with this disease. The following résumé of such lesions in reported cases and the subsequent report of a case will stress the various cutaneous manifestations that have been noted.

OCCURRENCE OF CUTANEOUS AND MUCOMEMBRANOUS LESIONS IN REPORTED CASES

The types of cutaneous and mucomembranous lesions described in the literature may be classified in five groups:

1. *Ulcerations and Granulomatous Involvement of the Oral Mucosa.*—There were 28 patients in the group with ulcerations and granulomatous involvement of the oral mucosa. In 10 instances the tongue was involved,[13] in 9 the larynx,[14] in 7 the mouth in general,[15] and in 2 the nasal septum was perforated.[16] H. capsulatum was demonstrated in most of these oral lesions either microscopically in sections of biopsy tissue or by culture.

In many instances the lesion of the tongue began as a solitary slightly indurated plaque on the upper surface of the tongue. There was no pain until ulceration occurred. It ultimately involved a large part of the tongue and was deep seated. In some cases the lesion on the tongue was the only apparent evidence of infection, while in others there was extensive involvement throughout the body.

The lesions of the larynx, vocal cords, epiglottis and posterior surface of the tongue were generally described as small discrete nodules, gray in color and somewhat dome shaped. They subsequently ulcerated, with associated pain and ultimate thickening or destruction of the involved organs.

In some patients with extensive systemic involvement, small ulcerated areas developed in the mucous membranes of the oral cavity. These areas were noted particularly a short time before death. In some instances the lesions would undergo involution and new ones would form after a short period of time. Perforation of the nasal septum was observed in an infant of 7 months and in a woman of 25 years.

2. *Papules, Plaques and Punched-Out Ulcers.*—These cutaneous lesions were observed in 11 patients[17] and measured 1 to 2 cm. in diameter. They generally began as papules or small plaques which had annular margins and depressed centers resembling lupoids or

13. The cases of Boltjes,[2d] Kemper and Bloom,[2g] Hansmann and Schenken,[3l] Palmer, Amolsch and Shaffer,[3v] cases A, D, ano E (of Parsons) cited by Parsons and Zarafonetis,[1] case H (of Stingily) cited by Parsons and Zarafonetis[1] and the cases of Henderson, Pinkerton and Moore[3g'] and Simson and Barnetson.[3l']

14. Alonso and Cancelo Freijo.[2b] Balina, Negroni, Bosq and Herrera.[3q] Palmer, Amolsch and Shaffer.[3v] Dean.[3w] Negroni.[3z] Parsons.[3d'] Brown, Havens and Magath.[3f'] Van Pernis, Benson and Holinger.[3j]

15. The cases of Boltjes,[2d] Hansmann and Schenken[3l] and Humphrey[3p] and cases A, B and D (of Parsons) cited by Parsons and Zarafonetis[1] and the case of Williams and Cromartie.[3k']

16. Case B (of Parsons) cited by Parsons and Zarafonetis[1] and the case of Agress and Gray.[3e']

17. The cases of Darling,[3l] Riehl,[3j] Clemens and Barnes,[3n] Balina, Negroni, Bosq and Herrera,[3q] Palmer, Amolsh and Shaffer,[3v] Negroni,[3z] Hansmann and Schenken[3a'] and cases B and E (of Parsons) cited by Parsons and Zarafonetis[1] and case G (of Steiner) cited by Parsons and Zarafonetis[1] and the case of Agress and Gray.[3e']

sarcoids. In most instances the lesions, which were single or multiple, subsequently ulcerated, leaving punched-out, ovoid, slightly infiltrated ulcers covered with hemorrhagic crusts. In some patients with these punched-out ulcers of the skin the disease apparently was present from eight to sixteen years before the ulcers developed. In the more fulminating types of histoplasmosis the ulcers appeared earlier. Histologic examination of biopsy material obtained from the borders of the ulcers usually established the diagnosis.

3. *Purpuric Lesions.*—Purpuric lesions were reported in 7 patients.[18] In 3, purpuric areas measuring from a few millimeters to 4 cm. in diameter were observed within a few weeks to several months before death. Some of the lesions subsequently ulcerated. The yeastlike cells of H. capsulatum were observed in material removed from the ulcers.

In 5 cases petechial hemorrhages developed over the chest and abdomen two or three days before death. Most of the patients in this latter group were infants.

4. *Abscesses, Furunculoid and Impetiginized Areas.*—Strong's [2a] patient had a chronic abscess on the wall of the chest with no other signs or symptoms. One of the patients reported by McLeod and his associates [21] had walnut-sized boils on the scalp. Organisms which in retrospect were believed to be H. capsulatum were demonstrated in material from the lesions of both patients.

An infant reported by Beamer and his associates [3y] had ". . . intact, ruptured or encrusted vesicles" 2 to 3 mm. in diameter all over the body from 4 days until 10½ months of age, at which time it died of histoplasmosis. The eruption was diagnosed as impetigo, with no record of cultural or histologic studies of the lesions. Rhodes and his associates [3l'] also reported the presence of "impetigo" on the face of a 3 month old infant with histoplasmosis. Iams [2q] stated that in an infant 3 months of age with histoplasmosis ". . . a peculiar pustular rash appeared on the chest and back, for which a diagnosis of pyoderma was made." No search was made for the organisms in the cutaneous lesions of these patients.

5. *Dermatitis, Local or Generalized.*—Shaffer and his associates [3k] reported scaling of the skin of the hands and feet in an 11 month old infant with histoplasmosis. De Almeida and da Silva Lacaz [3t] observed H. capsulatum in areas of verrucous dermatitis, and Negroni [3z] recovered the organisms from a patient with vegetating and ulcerated lesions.

Hansmann and Schenken [3l] observed a man 43 years of age who had an eruption for the last sixteen years of his life. It began in his

18. Schlumberger and Service.[2l] Shaffer, Shaul and Mitchell.[3k] Gunter and Lafferty.[3m] Humphrey.[3p] Anderson, Michelson and Dunn.[3r] Thomas and Morehead.[3x] Hild.[3n']

popliteal spaces and gradually involved his entire body during the next thirteen years. The skin was red, thickened and decidedly pruritic, and there was an associated enlargement of the superficial lymph nodes. Three months before death, hard umbilicated papules, 0.5 to 1.0 cm. in diameter, developed all over his body as well as in the tongue and oral mucous membranes. The fungus was observed in the skin and lymph nodes one and a half years before the papules developed. The authors expressed the belief that the infection was present throughout the course of the eruption and was not superimposed on the dermatitis.

The cutaneous lesions reported in patients with histoplasmosis are not sufficiently characteristic to permit one to make a positive diagnosis from the appearance of the involved skin alone. The causative organisms were readily demonstrated by microscopic examination and culture in biopsies from a surprisingly large number and variety of lesions. It is of interest that Schlumberger and Service [21] observed H. capsulatum in sections of normal-appearing skin removed at autopsy from a 3 month old child who had died of the disease.

The lesions diagnosed in infants as impetigo are of particular interest. In 1 instance the lesions developed when the child was 4 days of age and persisted until death, ten and one-half months later. Unfortunately, data relating to microscopic or cultural examinations of material obtained from these impetigo-like lesions have never been reported. The discovery of histoplasmosis in a premature infant a few months after birth [2q] suggests that the infection may have been acquired in utero.

The generalized pruritic eruptions of many years' duration described in patients with enlargement of superficial lymph nodes are indistinguishable from cutaneous involvements associated with lymphoblastomas. Undoubtedly in the past some patients with histoplasmosis and with generalized erythroderma have been given a diagnosis of lymphoblastoma.

HISTOPLASMOSIS AS RELATED TO RETICULOENDOTHELIAL DYSCRASIAS

When histoplasmosis is coexistent with another infectious granuloma caused by a specific organism it is usually impossible to determine microscopically which reaction is caused by H. capsulatum and which by the coexistent organism. This simultaneous occurrence of another pathogenic organism with the fungus is not rare. The second type of infection is often tuberculosis. Including the case which is presented in this report, there have been 5 instances in which the tubercle bacillus has been isolated in cases of proved histoplasmosis.[19] It is probable

19. Parsons and Zarafonetis.[1] Thomas and Morehead.[3x] Meleney.[3h']

that the progression of each disease was enhanced by the debilitating effect of the other, and it is likelier that in most instances it was the histoplasmosis which activated the previously dormant old focus of tuberculosis.

The association of histoplasmosis with neoplasms involving the reticuloendothelial system has not been infrequent. Histoplasmosis associated with leukemia has been reported twice,[20] and with Hodgkin's disease once,[1] and this is the second report of its occurrence with Hodgkin's disease, but accompanied with a malignant lymphoma. In case 47 of Parsons and Zarafonetis [1] a diagnosis of lymphosarcoma in a lymph node was made by biopsy, but after a complete autopsy at a later date, these authors discovered no evidence of lymphosarcoma and concluded that the original biopsy slide may have been from a different patient. Besides the interesting phenomenon of the simultaneous association of histoplasmosis with the malignant lymphoma, there is the added problem of confusing the histoplasmosis tissue reaction with that of the malignant lymphomas. No doubt, an occasional cell is encountered in histoplasmosis which, by itself, is indistinguishable from the Sternberg-Reed cell type. It is also evident that fibrosis and chronic inflammatory cells, particularly plasma cells and lymphocytes, are abundant in each disease. While focal areas of accumulations of polymorphonuclear cells and even necrosis will occasionally occur in Hodgkin's disease, they are not usually seen. Histoplasmosis would be more prone to present such pseudotuberculous structures. With such features in common, there is no doubt that histoplasmosis might be confused with atypical Hodgkin's disease. However, it should be distinguished from the classic pattern of actively neoplastic Hodgkin's disease and especially from so-called Hodgkin's sarcoma. In the presence of known histoplasmosis, rigid criteria must be maintained before a diagnosis of coincident Hodgkin's disease can be accepted. If the subsequent clinical picture and observations at autopsy support the diagnosis of a neoplastic disease and particularly if Hodgkin's disease assumes some of its more sarcomatous manifestations, the coexistence of the two diseases may be accepted.

PATHOLOGY

Reactions of tissue, both gross and microscopic, to the presence of H. capsulatum have been described and carefully studied by several authors. Histoplasmosis belongs to the general group of chronic infectious granulomas, and it possesses no specific cytologic characteristics which separate it from the other members of his group. The basic cell reacting to the presence of the fungus is the macrophage, and the

20. Riehl.[8j] Williams and Cromartie.[3k]

fundamental organ system involved is the reticuloendothelial system. There is little or no granulocytic reaction, and there are no signs of toxic injury to the surrounding stroma or parenchymal cells. The parasitized macrophages ordinarily possess no special structural characteristics, although an occasional one is multinucleated. These multinucleated cells have some resemblance to the Sternberg-Reed type of cell. At the time that the macrophage reaction is established, lymphocytes and plasma cells arrive in increased numbers. With the increase in accumulation of the reticuloendothelial elements there is subsequent vascular embarrassment, due mostly to the cellular crowding. When carried to an advanced degree this crowding leads to actual local necrosis. There is some fibroblastic reaction surrounding these areas of degeneration, and often typical Langhans giant cells are present. In the surrounding tissue macrophages are seen containing the organisms.

TREATMENT

There is no satisfactory treatment for a disseminated infection with H. capsulatum. The arrest of localized lesions has been reported. Strong's [2a] patient was well six months after a solitary abscess was thoroughly curetted and dressed with antiseptic preparations. The patient was not seen after that time. The patient reported by Mantell and his associates 3[o'] was asymptomatic six months after a course of treatment with the pentavalent organic antimony preparation stibamine glucoside ("neostam"). Ulcerations of the nostril and nasal septum of a man treated for nine months by Balina and his associates [2c] with sulfanilamide orally and sulfathiazole locally were healed. Alonso and Cancelo Freijo [2b] treated ulcerations of the pharynx, tonsils and larynx of a 59 year old man with sulfadiazine. The lesions healed in six weeks and were still well ten days following cessation of treatment.

An ulcer on the tongue of 1 of Meleney's [3h'] patients healed after treatment with radium, but recurred two years later. Roentgen therapy was then administered, and on return of the patient five years later the area was healed. Henderson and his associates [3g'] reported the involution of an ulcer on the tongue from radium implants. It had not recurred at the time of the patient's death several months later. Splenectomy and amputation have not been helpful. Bismuth compound, potassium iodide, thymol, quinine, penicillin and many other preparations have been used without benefit.

Seabury and Artis [21] carried out in vitro studies of susceptibility of the yeast phase of H. capsulatum. They observed that neoarsphenamine

21. Seabury, J. H., and Artis, D.: In Vitro Susceptibility of Histoplasma Capsulatum to Therapeutic Agents, Proc. Soc. Exper. Biol. & Med. **61**:15 (Jan.) 1946.

in a concentration of 100 mg. per hundred cubic centimeters and "stilbamidine" (4,4'-diaminostilbene) in concentrations from 10 to 100 mg. per hundred cubic centimeters prevented the growth of the organism, while sulfadiazine, sulfathiazole, "neostam," streptomycin and penicillin had no inhibitory effect in the amounts used.

The pentavalent antimony preparation "neostam" is of value in the treatment of kala-azar. In view of the fact that in tissue the fungus causing histoplasmosis resembles the protozoon which causes kala-azar, "neostam" has been used more than any other agent in the treatment of histoplasmosis. It was believed that while the organisms were of an entirely different nature, their localization in reticuloendothelial cells might denote a similar sensitivity to antimony. "Fuadin" N.N.R. (stibophen), a trivalent organic antimony preparation, and antimony potassium tartrate, an inorganic salt of antimony, have also been advised for the treatment of this disease. "Neostam," sulfadiazine and penicillin were used unsuccessfully in the treatment of our patient.

It will be difficult to evaluate the results of treatment until more is known about the course of the disease. In practically all the recognized cases the disease has had a fatal outcome. There may be a benign form of the disease similar to that observed in coccidioidomycosis. For this reason, if treatment is given to a patient with active lesions and healing results, it cannot be concluded that improvement was due to the treatment or that the patient has been cured.

REPORT OF A CASE

D. C., a farm laborer aged 37, was referred to the Clinic of the University of California Medical School in December 1943.[22] He was born in South Dakota and first came to California in 1938, but did not reside there permanently until 1943. He had done agricultural work in North and South Dakota and in many of the Western states from 1931 to 1943. He had been well until the fall of 1937, when he noticed a swelling on the left side of his neck. In February 1938, a cervical node was removed, and a pathologist made a diagnosis of Hodgkin's disease. From 1938 to 1943, courses of roentgen therapy were given to control pain in the chest, back and inguinal regions. There were no other constitutional symptoms until 1942, when there was some loss of weight following an episode of chills, fever and abdominal pain. The patient recovered slowly in the next three months and was able to resume his work. In July 1943, a nodule appeared in the center of the tongue. The nodule increased in size, and at the end of three months ulceration occurred, which was not painful.

The patient, first seen by us in the outpatient department in December 1943 (six years after the onset) appeared poorly nourished, but not acutely ill. Small discrete nontender nodes were observed bilaterally in the cervical, axillary and inguinal regions. The mouth was edentulous. In the middle of the tongue was an ulcer 1.5 cm. in diameter, with a shallow depressed base and a rolled firm margin. The spleen was not palpable, and the edge of the liver was felt just below the

22. A report of a case has appeared in the Archives (**52**:130 [Aug.] 1945).

xiphoid process. Roentgenograms of the chest showed a group of nodes in the midline below the arch of the aorta, but no other abnormalities. Numerous encapsulated yeastlike bodies contained within mononuclear cells were observed in stained smears of tissue removed from the edge of the ulcer of the tongue. A tentative diagnosis of histoplasmosis was made and then definitely confirmed on Jan. 26, 1944, when colonies of H. capsulatum were observed in cultures which previously had been inoculated with scrapings of tissue from the ulcer. Sections of the cervical lymph node, removed elsewhere in 1938, were obtained, and, after a long search, a mononuclear cell was seen containing three pale-staining inclusions resembling the organisms observed in the tissue of the tongue.

The patient was admitted to the University Hospital on Jan. 18, 1944 for further investigation.

Laboratory studies gave the following results: The Wassermann and Kahn reactions of the blood were negative. The blood count and urine were essentially normal. The serum protein totaled 12.07 Gm. per hundred cubic centimeters (albumin 4.3 and globulin 7.77). The serum calcium was 8.8 mg. and phosphorus 3.04 mg. per hundred cubic centimeters. Aspirated marrow showed a normal

Fig. 1.—Histoplasmosis of the tongue.

count. H. capsulatum was not recovered in cultures of the sternal bone marrow or in repeated blood cultures. Several Giemsa-stained thin and thick blood smears were examined, but the yeast phase of the fungus was not observed. Intradermal tests employing histoplasmin, coccidioidin and haplosporangin were performed on January 24, but only equivocal reactions occurred. Microscopic examination ultimately revealed the characteristic yeast cells of the fungus in sections of an extirpated axillary lymph node. However, the fungus did not develop in cultures inoculated with material from this same lymph node. Sputum cultures made on January 27 were likewise negative.

From January 28 to February 11, sulfadiazine was given orally in increasing doses from 4 to 12 Gm. daily, the blood level reaching 15.8 mg. per hundred cubic centimeters on February 11. On February 4, scrapings of the lesion of the tongue again were taken and positive cultures were still obtained. In mice inoculated with some of this same material a widespread infection with H. capsulatum developed. There was no improvement in the appearance of the ulcer of the tongue, nor was there any reduction in the temperature range of 36 to 39 C.

During the following month, there was a gradual increase in the size of the ulcer and microscopic examination of the necrotic tissue indicated that numerous organisms were still present. From March 17 to 29, during a course of roentgen therapy, a total of 1,000 r was given to the left half of the ulcer. No appreciable effect was noted. The generalized lymphadenopathy had not changed. The spleen was not palpable, and the liver was felt 4 cm. below the xiphoid process. Tests of hepatic function showed some impairment.

From April 8 to 14, a total of 4.2 Gm. of "neostam" was given intravenously. Daily oral doses of 6 Gm. of para-aminobenzoic acid were administered concurrently to prevent hepatic damage. Loss of weight, mild anemia and leukopenia (4,200 leukocytes) were noted during this period. However, on May 5 the results of the tests of hepatic function were normal. There was no change in the ulcer of the tongue. The usual intermittent fever continued and was augmented by febrile responses up to 40 C. (104 F.) as a result of the injections of "neostam" given every other day.

On May 11, sternal marrow and blood cultures were again negative. Reactions in intradermal tests employing an antigen prepared with the fungus isolated from the patient were negative, although a complement fixation test utilizing the same antigen elicited a positive reaction.

On May 19, penicillin was given by the intravenous drip method, despite the fact that laboratory tests demonstrated that the fungus isolated from the patient was not sensitive to it. A total of 1,300,000 units was given in eleven days. The intermittent fever was unchanged. The tongue was becoming painful, and the ulcer increased in size. This was still the only evident lesion from which the organism could be readily demonstrated in direct smears, in biopsy and by culture. The liver had increased in size, reaching the umbilicus. The spleen was not palpable. Loss of weight was slow but progressive, influenced perhaps by the difficulty in eating, although a stomach tube was used because of pain in the tongue. Terminal bronchopneumonia developed, followed quickly by coma and death on June 8, 1944.

Biopsy of Cervical Lymph Node (removed elsewhere February 1938, but first examined by us in December 1943).—The general outline of the lymph node was well preserved. However, examination for detail of pattern showed an obliteration of the sinusoids in the lymph node by an increased number of cells of the lymphocytic type. Some round cell reaction was noted, particularly of the plasma cell type, but no eosinophils were encountered. Fibrosis was not prominent, and the capsule of the lymph node was not invaded. Macrophage reaction was not evident, and no formation of tubercles, necrosis or Langhans type of giant cell was seen. Scattered throughout the node were large cells of reticuloendothelial type having multiple nuclei, which in some instances were lobulated and which not infrequently had a prominent central nucleolus. These cells had a somewhat darkened, usually eosinophilic cytoplasm, and extensive pleomorphism within these cells was observed. At the time of the initial study H. capsulatum was not seen in any of the cells. However, exhaustive search at a much later date did reveal one small relatively normal-appearing macrophage that contained three structures microscopically characteristic of the fungus. The diagnosis was a cervical lymph node with cellular reaction microscopically characteristic of Hodgkin's paragranuloma and containing H. capsulatum.

Biopsy of Tongue (December 1943).—The superficial epithelium was ulcerated, revealing underlying chronically inflamed connective tissue, showing masses of round cells and some proliferation of connective tissue. Scattered throughout

were large numbers of macrophages, many of which contained masses of yeast cells. No actual caseation and no formation of tubercles were observed. The pleomorphism of the macrophages was not prominent, and there was no cellular proliferation which even vaguely suggested neoplastic processes. An occasional Langhans giant cell was encountered which was heavily parasitized. The diagnosis was chronic ulcer of the tongue containing H. capsulatum.

Biopsy of Axillary Lymph Node (January 1944).—The greater portion of the axillary lymph node was completely replaced by caseous material having all the

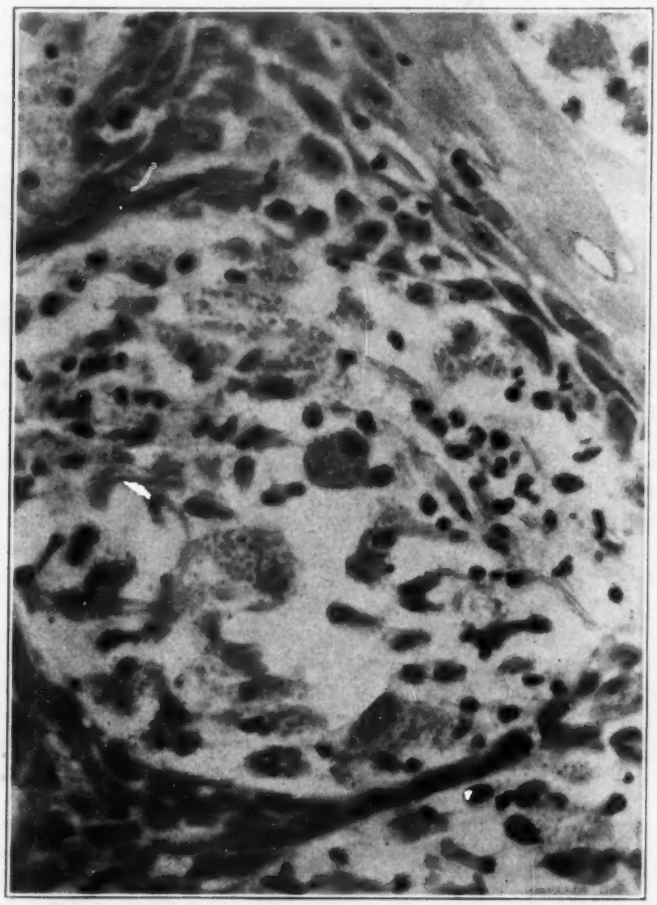

Fig. 2.—Histoplasma capsulatum in a section of the tongue. × 500.

morphologic characteristics of an old tuberculous focus. In one area, the node had not been involved by this apparent tuberculous reaction, but instead showed increased numbers of chronic inflammatory cells with a definite predominance of the macrophage type. Many of these macrophages appeared to be rather foamy, with some tendency to lie in syncytial masses, but no actual formation of tubercles was present. Caseation and necrosis were absent in this portion of the lymph node, and no Langhans giant cells were encountered. Some fibrosis was present, and in

scattered macrophages morphologically characteristic histoplasma organisms were noted. These macrophages contained only one to three organisms and never large masses of them. An occasional macrophage was multinucleated and did not have a prominent nucleolus, so that it was morphologically identical with the so-called Sternberg-Reed cell seen in Hodgkin's disease. However, the definite chronic granulomatous pattern of this portion of the lymph node with the distinct predominance of the macrophage type of cell lent an over-all microscopic picture which in no way suggested the presence of Hodgkin's disease. The diagnosis was a lymph node containing an old focus of tuberculosis and a granulomatous reaction revealing H. capsulatum.

Fig. 3.—Histoplasma capsulatum in a section of the tongue. × 1,000.

Report of Autopsy.—Only pertinent observations of the autopsy performed in June 1944 will be discussed.

Examination of the body revealed advanced wasting of all the tissues. The mouth was normal except for the tongue, on which was seen an indurated ulcer 0.5 cm. deep and 3 cm. in diameter. The lymph nodes were not significantly enlarged. The heart was within normal limits in size and structure. Each pleural cavity contained about 1,000 cc. of straw-colored clear fluid and was free of adhesions. Both lungs were moderately congested and showed bilateral apical scarring, characteristic of old tuberculous foci. In addition, there were necrotic-appearing nodules 2 to 3 mm. in diameter, resembling small tubercles, which were scattered widely throughout the lungs. The hilar lymph nodes were small, but grossly caseous. The liver weighed 2,300 Gm. and was studded throughout by multiple

nodules 1 to 5 mm. in diameter, similar in appearance to the nodules seen in the lungs. The spleen weighed 920 Gm. and was grossly not remarkable except for the presence of similar nodules. The intestinal tract was normal except for two grossly caseous mesenteric lymph nodes 1 cm. in diameter. The adrenal glands had no gross abnormalities. The kidneys weighed 240 Gm. each and were grossly normal except for the tubercle-like structures present in infrequent numbers. The brain weighed 1,500 Gm. and grossly presented no abnormalities.

Microscopically all of the small tubercle-like structures had the architecture of a typical early tubercle. In this structure, the Langhans giant cells were not abundant and were often poorly formed. The tubercle was not well walled off, and it appeared to be moderately exudative. The macrophage reaction, although present, was obscured by the exudate, which centrally was not of the classic caseous type but had quite a few degenerated nuclear fragments and scattered granulocytes. There had been little conglomeration of any of these structures. Acid-fast stains revealed tubercle bacilli. In the lymph nodes from the autopsy the tuberculous reaction appeared more mature, with well defined surrounding fibrosis and fully mature Langhans giant cells. Near these older areas of tuberculous reaction a few early tubercles of the miliary type were encountered, but no yeast cells of H. capsulatum were observed. There was no suggestion of histoplasmosis in any of the sections of tissues obtained at autopsy, except in the tongue, and these sections showed a process identical with that described in the biopsy taken in December 1943.

Besides the tuberculous reaction already described, the liver and spleen showed still another local type of reaction which was neoplastic. These foci were decidedly cellular and were microscopically not inflammatory in type. No caseation was seen here, acid-fast bacteria were not present and Langhans' giant cells were absent. There were closely packed nonencapsulated sheets of cells, which were often multinucleated and which showed a great deal of pleomorphism and active mitotic proliferation. Individual cells were large and had a lightly eosinophilic ill defined, rather abundant cytoplasm, which often contained more than one nucleus. The nuclei were prominent and vesicular in type and had a clearcut but not heavy nuclear membrane. Often a central, rather large and occasionally eosinophilic nucleolus was seen. Besides these prominent giant cell forms having as many as a dozen nuclei, there was seen a background of reticuloendothelial type of cell and scattered typical lymphocytes. Fibrosis was not particularly prominent. Eosinophils were not seen, but scattered polynuclear granulocytes and plasma cells were in evidence. This clearly neoplastic process was composed of malignant derivatives of the reticuloendothelial system. It could be classified as a type of primitive "stem cell" lymphosarcoma. However, it is believed that the term Hodgkin's sarcoma best fits this pleomorphic picture. The neoplastic tissue was seen only in the liver and spleen. The adrenal glands were microscopically not remarkable, and the tissue of the brain was within normal limits. H. capsulatum was recovered in cultures of the cardiac blood, but not in cultures of spleen and liver pulp, bile, urine and fluids aspirated from the peritoneal, pleural and pericardial activities.

The final pathologic diagnosis was: (1) histoplasmosis of the tongue with extension to the cervical and axillary lymph nodes and terminal invasion of the blood stream, (2) malignant lymphoma (probably best classified as a Hodgkin disease type) involving cervical lymph nodes, spleen and liver and (3) old tuberculosis of the pulmonary and hilar lymph nodes with subacute miliary dissemination to lungs, liver, spleen, lymph nodes and kidneys.

Laboratory Diagnosis.—Direct examination of material removed from suspected lesions may result in an immediate diagnosis of histoplasmosis. With our patient the characteristic yeastlike cells readily could be seen in stained preparations of material scraped from the periphery of the lesion of the tongue. In such preparations the organism is seen in large mononuclear or epithelial cells and appears as a small oval body, 1 to 4 microns in length and surrounded by a nonstaining capsule. The deeply staining chromatin material of the cell is concentrated in a crescent-shaped mass at one pole of the organism, giving a signet ring appearance to the parasite. In dried stained impression smears of biopsy material and in sections of tissue the fungus may be confused with the leishmania stage of Leishmania donovani, Leishmania tropica or Leishmania braziliensis, the protozoan parasites causing visceral, cutaneous and American leishmaniasis, respectively. The presence of a rod-shaped kinetoplast and absence of a capsule are characteristics of the Leishmaniae which serve to differentiate these organisms from the yeastlike cells of H. capsulatum.

Although a provisional diagnosis may be established on the basis of finding the organisms in thick or thin smears of peripheral blood, in smears of sternal bone marrow, in smears or sections of biopsy specimens or in splenic pulp obtained by puncture, every effort should be made to confirm the observations by isolation of the fungus in cultures. H. capsulatum will develop in a variety of laboratory mediums. Sheep blood agar, Sabouraud's dextrose agar, Peppler's[23] buffered medium and beef heart hormone broth and agar containing cystine monohydrochloride and sodium sulfite were the mediums most frequently employed for the isolation of the fungus from specimens obtained from our patient as well as for the preparation of antigens for serologic and intradermal tests. In most instances plates, flasks or slants were inoculated in pairs, one of the cultures incubated at 37 C. and the other kept at room temperature. Primary isolation of the fungus from tissue fragments and biopsies was most effectively obtained on sheep blood agar plates kept at room temperature. On this medium young colonies of H. capsulatum are small, slightly raised, rough, dull appearing and dark brown and have an irregular edge. A period of growth of five to seven days is required before the colonies acquire an appreciable size and develop differential characteristics. Microscopically the young colonies show branching septate hyphae on which are borne small (3 to 6 microns in diameter) spherical or pyriform spores with smooth walls. These arise directly on the walls of the hypha or on short stalks. With continued growth the colony develops a typical fungous appearance with the production of a white cottony aerial mycelium in from nine to fourteen days. Microscopically this older colony shows spherical, oval or pyriform smooth-walled spores, varying considerably in size (5 to 18 microns in diameter), and large (18 to 25 microns in diameter) tuberculate, spherical or pyriform spores, containing one or several usually round fat globules. The protuberances of these tuberculate spores may reach 6 to 8 microns in length. Both of these spore types may be sessile or pedicellate. The mycologic diagnosis of histoplasmosis is based primarily on the presence in cultures of the large tuberculate spores. This characteristic morphologic feature of H. capsulatum serves to differentiate this fungus from others possessing similar mycelia and spores.

The yeast phase of the fungus was obtained in culture by inoculating blood slants with young colonies picked from blood plates kept at room temperature. The slants were sealed with "parafilm" and incubated at 37 C. Serial transfers

23. Peppler, H. J.: Routine Procedures for the Isolation and Identification of Certain Pathogenic Fungi, Tech. Bull. Registry of M. Technologists **4**:123, 1943.

were made at five day intervals. An abundant staphylococcus-like growth was obtained, and microscopic examination showed small budding oval yeastlike bodies, closely resembling the parasitic forms seen in tissues. Although the yeast cells predominated in such cultures, a small amount of hyphal growth was invariably present. Unsealed blood slants maintained at room temperature developed the characteristic aerial mycelial growth.

Necrotic tissue obtained by gently scraping the borders of the lesion on the tongue was ground in a mortar with isotonic solution of sodium chloride and sand. The resulting suspension was inoculated intraperitoneally into 3 mice. One of the mice died after seventy-nine days, the second was killed after eighty-two days and the third died ninety-two days after inoculation. Postmortem examinations were performed, and greatly enlarged livers and spleens were observed in all the animals. Blood plate cultures, Giemsa-stained impression smears and histologic sections of these organs revealed that an overwhelming infection with H. capsulatum had developed in the mice.

Two types of antigens for use in the complement fixation test were prepared with the fungus isolated from the patient, one employing the mycelial phase and the other the yeast phase of the organism. For the preparation of the mycelial phase antigen, it was discovered, after the trial inoculation of several types of liquid mediums, that the beef heart hormone broth produced the most rapid and luxuriant growth of the fungus. Flasks with a capacity of 500 cc. containing 200 cc. of the broth were inoculated with 0.5 cc. of a saline suspension of yeast phase growth scraped from blood slant cultures, which had been sealed with "parafilm" and incubated at 37 C. The inoculated flasks were kept at room temperature for forty-six days. Phenol was then added to give a final concentration of 0.5 per cent, and the flasks were incubated at 37 C. for forty-eight hours. The contents of the flasks were first filtered through paper and then run through a Seitz filter. The filtrate was bottled, tested for sterility and stored in the refrigerator. The yeast phase antigen was prepared by inoculating Roux flasks (with metal or plastic screw tops) containing beef heart hormone agar with 1 cc. of a saline suspension of yeast phase growth from a sealed blood slant culture. The flasks were incubated for eight days at 37 C., and all those showing an abundance of mycelial growth were discarded. The growth in each flask was washed off the agar surface with 25 cc. of buffered saline suspension (p_H 7) containing 0.5 per cent phenol. Sterile glass beads dropped into the flasks greatly facilitated removal of the growth. The phenol saline suspension of the yeast phase growth was incubated at 37 C. for forty-eight hours, tranferred to large tubes and centrifugalized. The clear supernatant fluid was filtered through a Seitz filter, bottled, tested for sterility and stored in the refrigerator. The procedures followed for the preparation of the intradermal test antigen were identical with those employed in the preparation of the mycelial phase complement fixation antigen noted previously. However, the beef heart hormone broth cultures in this instance were incubated at a temperature of 28 C. and phenol added at the end of an incubation period of sixteen days.

Quantitative complement fixation tests were performed with the patient's serum, employing both the mycelial phase and yeast phase antigens. The results obtained follow:

Serum dilutions	1:2	1:4	1:8	1:16	1:32
Yeast phase antigen diluted 1:4	++++	++++	+++	+++	++
Mycelial phase antigen diluted 1:4	++++	+++	++	+	—

To eliminate the possibility of false reactions caused by the culture medium, control tests were performed with the phenolized beef heart hormone broth. The reactions were negative.

The cutaneous sensitivity of the patient was tested by the intradermal injection of 0.1 cc. of a 1 to 100 dilution of each of the following antigens: three lots of histoplasmin designated as 1, 2 and 3, one of coccidioidin and one of haplosporangin.[24] There were no immediate reactions. The accompanying table shows the reactions observed in twenty-four and forty-eight hours:

Cutaneous Sensitivity to Intradermal Injection of Antigens

Antigen	Area Affected (Mm.)	
	After 24 Hours	After 48 Hours
Histoplasmin 1	8 *	8 *
Histoplasmin 2	10 †	10 †
		19 *
Histoplasmin 3	6 *	6 *
Coccidioidin	6 †	5 *
Haplosporangin	13 †	8 †

* Erythema.
† Edema.

If only those tests were considered positive which showed an area of edema 5 mm. or more in diameter, it will be seen that histoplasmin 2, coccidioidin and haplosporangin elicited positive reactions. In those instances in which erythema occurred without induration the reactions were considered negative.

When antigen prepared from the patient's own strain of H. capsulatum became available the patient was tested intradermally with a series of dilutions. To eliminate any possibility of false reactions, control tests were performed with corresponding dilutions of phenolized beef heart hormone broth. At intervals during a twenty day period the patient was tested with 0.1 cc. injections of the 1 to 10,000, 1 to 1,000 and 1 to 100 dilutions of both the antigen and control fluid. In addition undiluted antigen and control fluid were employed. When the reactions were observed after twenty-four and forty-eight hours it was observed that all were negative. However, the undiluted antigen produced an immediate response, although no delayed reaction occurred. The potency of this antigen may be questioned in view of the comparatively short period of incubation which was utilized during its preparation.

Since there are some rather striking similarities between histoplasmosis and visceral leishmaniasis (kala-azar), it was decided to perform Napier's serum test with the patient's serum. This simple test is widely employed in endemic regions for the diagnosis of kala-azar. It is performed by adding 1 drop of commercial formaldehyde to 1 cc. of the patient's serum in a small test tube. A tube containing the same amount of normal serum is used as a control. The tubes are shaken and allowed to stand at room temperature. A positive reaction is obtained if the mixture in the tube becomes solid and opaque within thirty minutes. According to these standards the reaction with our patient's serum was negative since, although solidification occurred in fifteen minutes following the addition of the drop of formaldehyde, the mixture did not become opaque until two hours and fifteen minutes later. The control serum did not solidify or become opaque within twenty-four hours.

24. All of the lots were supplied by Dr. Charles E. Smith of the Stanford Medical School.

Wolff's [25] precipitation test was also performed with the patient's serum. This simple serologic procedure is employed in the diagnosis of malaria and, according to the originator, kala-azar is the only other infection in which positive reactions regularly occur. The test is based on the precipitation of the euglobulin fraction of the serum by buffer solutions. Only two solutions are employed in the test, one a test buffer solution and the other a control solution. The presence of varying amounts of precipitate in the "test" tube indicates a positive reaction. With our patient's serum a definite precipitate formed in the "test" tube, whereas the control tube remained clear.

Comment.—The patient had a somewhat benign type of histoplasmosis with involvement of the cervical and axillary lymph nodes and tongue and a terminal invasion of the blood stream. The diagnosis was made by biopsy of the lesion of the tongue five months before death. Death probably was due to disseminated miliary tuberculosis. It is not unlikely that the roentgen ray therapy given to various parts of the body may have contributed to the terminal miliary dissemination of the tuberculous process. A malignant lymphoma, best classified as a variant of Hodgkin's disease, was coexistent.

The clinical appearance of the ulcer on the tongue was suggestive of tuberculosis or syphilis. The initial nodule was firm in consistency and not painful until sometime after ulceration developed. The location of the lesion on the middorsal surface of the tongue was more suggestive of syphilis than tuberculosis. It might have been possible to cure it with larger amounts of roentgen rays.

SUMMARY

A study of 88 cases of histoplasmosis reported in the literature reveals that cutaneous or mucomembranous lesions were present in 45, or about half the number. Histoplasma capsulatum was observed in a large percentage of these cutaneous lesions.

The cutaneous and mucomembranous lesions described in the reported cases fall into five distinct groups: (1) ulceration and granulomatous involvement of the oral mucosa, (2) papules, plaques and punched-out ulcers, (3) purpuric lesions, (4) abscesses, furunculoid and impetiginized areas and (5) local or generalized dermatitis.

An additional case of histoplasmosis is reported in a man in whom an ulcer of the tongue developed. The diagnosis was established five months before death on isolation of the fungus in cultures of biopsy tissue from the walls of the ulcer. In addition to the involvement of the tongue, the patient had histoplasmosis of the cervical and axillary lymph nodes with a possible terminal invasion of the blood stream by the parasite. He had associated Hodgkin disease of five years' duration and disseminated miliary tuberculosis, which probably caused his death. Treatment with sulfadiazine, stibamine glucoside, ("neostam") and penicillin was of no value. The mycologic, histologic and postmortem observations are described in detail.

25. Wolff, E. K.: The Buffer Precipitation Test for Malaria (B.P.T.) Adjusted for Large Scale Examinations, Indian M. Gaz. **75**:517 (Sept.) 1940.

Histoplasmosis has been observed to be coexistent with tuberculosis, leukemia and Hodgkin's disease. While histoplasmosis may simulate Hodgkin's disease microscopically, our patient had coexistent Hodgkin's disease, as indicated by the clinical course of the disease and by the discovery at autopsy of a malignant lymphoma, best classified as so-called Hodgkin's sarcoma.

A diagnosis of histoplasmosis cannot be made on clinical signs alone. Biopsy of skin or of lymph nodes is the most successful method of diagnosis during life. Examination of blood smears, bone marrow and splenic pulp obtained by puncture may be of value, but in all instances the diagnosis must be confirmed by isolation of the fungus in culture. Intradermal and complement fixation tests may be helpful. In our patient the histoplasmin, coccidioidin and haplosporangin tests gave equivocal results. The reaction to Napier's serum test was negative and to Wolff's precipitation test positive.

The sources of infection, the modes of transmission and the portals of entry of H. capsulatum are not known. Animal to man or man to man transmission may occur. Pulmonary calcification may be due to a benign infection with H. capsulatum, but cross reactions with histoplasmin, blastomycin, coccidioidin and haplosporangin prevent such an assumption now.

There is no satisfactory treatment for a disseminated infection with H. capsulatum. Arrest of some localized lesions has been reported with various remedies. "Neostam," sulfadiazine, penicillin and roentgen ray therapy were unsuccessful in our patient.

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ABSTRACT OF DISCUSSION

DR. JAMES H. MITCHELL, Chicago: I should like to report a case which has not been published and which should be added to the number already reported by Dr. Miller. The patient, a woman, was seen two years ago. She had spent the winter in Florida. She returned to Chicago in failing health and was a patient of Dr. William Thomas of the Presbyterian Hospital. He referred her to Dr. Vernon David for operation on the gallbladder. Dr. David, however, refused to operate because of her condition, which was poor. She had all the signs and symptoms, such as anemia, leukopenia, enlarged spleen and oscillating temperature, and had lost a great deal of weight.

I was asked to see her because she had a generalized papular eruption. These papules were suggestive of tuberculids of the ulcerated type.

She had a productive cough, and the roentgenograms of the lungs indicated a great deal of activity of one kind or another, but no diagnosis was made by the roentgenologist.

The patient was so ill that I hesitated to do a biopsy, but, nevertheless, this was done. There was a symmetric generalized distribution of papules with a lesion in the left labial commissure similar to the lesion described by Palmer, Amolsch and Shaffer.[3v] The preliminary diagnosis given by the pathologist before I saw the section was "nonspecific inflammatory reaction," but before I

had an opportunity to examine the section he changed his diagnosis to that of blastomycosis. The pathologist is to be excused on the ground that unless one is on guard and has an eye for the mycoses one can easily miss the observations in a section of this disorder. This fact was clearly demonstrated to me when I gave the sections for autopsy to the postgraduate students in mycology. The case was discussed at length before the sections were passed out for examination, but not one of the students was able to see the organism unaided.

Shortly after the biopsy specimen and positive cultures were obtained the patient died, and an autopsy was performed. All treatment had been without results.

I have lantern slides of all the tissues, but I will show only a few. (Slides were shown.) The first slide is a low power photomicrograph of the biopsy specimen of the skin. There is to be seen a decided inflammatory reaction with a small area of ulceration at the surface. The second slide is a high power photomicrograph of the center of this ulcerated area, showing the phagocytosed capsulated organisms in large numbers. A smear made of this ulcer would probably have made it possible to demonstrate the presence of the organisms, but this was not done. The third slide shows a section of the adrenal gland, which is commonly involved.

The next slide shows a colony of the mycelial form of the organism, which can be transformed into the yeastlike organism by various means, one of which consists of growing the organisms on sealed blood agar tubes at 37 C. The results, however, are variable and are not to be depended on. The next slide shows the yeastlike form. I have photographs of the mycelial form emerging from the yeastlike form. The last slide shows the large tuberculate spore which is necessary for the identification of the culture.

Dr. Martin F. Engman Jr., St. Louis: You perhaps noticed on the map that Dr. Miller showed that St. Louis is right in the middle of the area where there have been numerous cases. Dr. Morris Moore, mycologist to the Barnard Free Skin and Cancer Hospital, has been interested in this disease and has seen about 18 patients. Reports of some of the cases have been published. His latest report of a case was published recently with Dr. Louis H. Jorstad in the *Annals of Otology, Rhinology and Laryngology.* In this report there is a fairly complete review.

This disease is of importance to dermatologists, particularly in the differential diagnosis of obscure lesions in the mouth. Of Moore's patients about a third had either mucomembranous or cutaneous lesions. In the mouth the lesions may be ulcers, plaques or granulomas of no specific type.

The disease is constitutional and spreads via the reticuloendothelial system. Regional lymph nodes become involved and may imitate Hodgkin's disease. Caseation in the lungs or the adrenal glands may occur and thus simulate tuberculosis. Sometimes histoplasmosis and tuberculosis occur together.

Dr. Miller deserves to be congratulated for his study of this disease and for bringing it to our attention. Undoubtedly we will, many of us, encounter such cases.

Dr. George M. Lewis, New York: In a patient recently observed and studied, the clinical symptoms and signs favored the diagnosis of histoplasmosis. The patient had ulcerating lesions of the tongue, splenomegaly, hepatomegalia, enlarged lymph nodes and irregular fever, with a downhill course in which the patient rapidly lost weight.

This patient was treated with sulfadiazine, penicillin and various other drugs prior to the opportunity which my associates and I had to make intensive studies. This led us to pursue various investigations with perhaps more avidity and thoroughness than usual. Everything which we tested gave negative results. I should like to ask Dr. Miller to say when he closes whether in this case he followed the patient after considerable treatment with the idea that the organisms were destroyed in the available tissues, and I should also like to ask whether the leukopenia was constant throughout.

The diagnosis of histoplasmosis is not always easily made, in spite of the reproductions that Dr. Miller and Dr. Mitchell have shown. I think that both of the discussers deserve credit for arriving at a definite diagnosis prior to death. We know that most of the published cases are found at autopsy.

We should be on the lookout for these cases, which are undoubtedly more numerous than the published number would lead us to believe.

DR. FREDERICK R. SCHMIDT, Chicago: I was interested in Dr. Miller's presentation because of my experience with the differential diagnosis of these tumors. About two years ago, in conjunction with a pathologist, Dr. Tuda, I reported 3 cases of so-called myoblastoma, in which we observed a nodule on the tongue, with ulcers on the skin similar to those in the pictures shown by Dr. Miller.

When we first saw the sections, we thought that the large vacuolated cells were those of histoplasmosis, but after eliminating that possibility, we did not know what they were until we saw an article by Klemperer in which were pictures of an abnormality similar to that in our patients. I do think, especially in the differential diagnosis of nodules of the tongue, that we should also consider so-called myoblastomas.

DR. HIRAM E. MILLER, San Francisco: I wish to thank the men who have discussed this presentation, especially Dr. Mitchell for giving some of the cultural characteristics of the organism which time prevented me from giving.

In answering Dr. Lewis, the presence of organisms was substantiated by smears, cultures or biopsy after each type of treatment and at other regular intervals. They continued to be observed in increasing numbers throughout the course of the disease.

Blood counts were essentially normal when the patient was first observed, but leukopenia developed when he began to lose weight, and it persisted until his death.

As Dr. Montgomery has brought out (Dr. Montgomery requested that his discussion of this paper be omitted from the record), there are several organisms that are closely related to Histoplasmosis capsulatum, and these have been reported by many observers. This is especially true in animals. Organisms resembling H. capsulatum have been observed in the dog, in the mouse and in a ferret, but only in the dog has it been specifically identified by its cultural characteristics. The dog, as a domestic pet, could serve as a reservoir for the infection. The report by McLeod of 2 cases of histoplasmosis in brothers who slept together may be an example of man to man transmission of the disease.

I feel reasonably certain that I have made a diagnosis of lymphoblastoma in patients with generalized cutaneous eruptions who may possibly have had histoplasmosis. In the final analysis, lack of knowledge of the disease is the main reason for not making a correct diagnosis.

POIKILODERMA VASCULARE ATROPHICANS

Report of a Case with Observations at Autopsy

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ATROPHY, telangiectasia and pigmentation, with muscular weakness, were described by Petges and Cléjat [1] in 1906, the same year in which Jacobi [2] described a complex dermatologic disease characterized by telangiectasia, pigmentation and, later, capillary hemorrhages and atrophy, which he [3] subsequently termed poikiloderma vasculare atrophicans. Since then over 180 cases have been presented, both as published reports and in addresses before dermatologic societies. Lane [4] introduced the first case to an American audience in 1920, before the New York Dermatological Society. During the last twenty-five years, approximately twenty-two papers describing this disease have appeared in the English and American literature.

In recent years the existence of poikiloderma vasculare atrophicans as a separate clinical entity has been challenged by many competent dermatologists, including Oppenheim [5] and Montgomery and Sullivan.[6]

From the Boston City Hospital, Department of Dermatology and Syphilology, and the Mallory Institute of Pathology.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 12, 1946.

1. Petges, G., and Cléjat, C.: Sclérose atrophique de la peau et myosite généralisée, Ann. de dermat. et syph. **7**:550, 1906.

2. Jacobi, E.: Fall zur Diagnose (Poikilodermia atrophicans vascularis), Verhandl. d. deutsch. dermat. Gesellsch. **9**:321, 1907.

3. Jacobi, E.: Poikiloderma Atrophicans Vascularis, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1908, pt. 3, p. 95.

4. Lane, J. E.: Poikiloderma Atrophicans Vasculare, with Report of a Case by Oliver S. Ormsby, Arch. Dermat. & Syph. **4**:563 (Nov.) 1921; Poikiloderma Atrophicans Vasculare: Conclusion of Previously Reported Case, ibid. **8**:373 (Sept.) 1923.

5. Oppenheim, M.: Atrophien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 500.

6. Montgomery, H., and Sullivan, R. R.: Acrodermatitis Atrophicans Chronica, Arch. Dermat. & Syph. **51**:32 (Jan.) 1945.

These authors expressed the belief that this is a symptom rather than a clinical entity. According to Montgomery and Sullivan, Oppenheim did not regard the poikiloderma vasculare atrophicans of Jacobi as a real clinical or histopathologic entity, but stated the belief that some cases should be classified as acrodermatitis chronica atrophicans, others as poikilodermatomyositis and still others as secondary to various dermatoses. They concurred with this view. McCarthy [7] presented a detailed histologic description of poikiloderma. Weidman [8] used the pathologic diagnosis of poikiloderma vasculare atrophicans in classifying the material studied by him at the Laboratory of Dermatologic Research of the University of Pennsylvania.

Various types of this disease, including both localized forms and the generalized form, have been presented in the literature. Among the former, two types of pigmentated dermatoses have been described—Riehl's melanosis and Civatte's *poikilodermie réticulée pigmentaire du visage et du cou.*

Hollander [9] stated that the term "Riehl's melanosis" should be reserved for the cases that were observed at the end of World War I and were first described by G. Riehl of Vienna. Riehl [10] reported cutaneous discolorations of bronze to chocolate color, localized on the face, especially the forehead, zygomatic region and temples, and spreading to the neck, ears (anterior and posterior auricular region) and scalp. The extensor surfaces of the forearms and hands and the axillary, mammary, umbilical and inguinal regions were rarely affected. The pigmentation started with discrete spots of various sizes, which later developed into diffuse melanotic areas. There were frequently white depigmented spots between the dark maculas. Numerous perifollicular macular or papular lesions, first reddish brown and later dark brown, could sometimes be seen. The skin was rough and somewhat scaly and looked as though it were covered with flour dust. Furthermore, numerous dilated follicular orifices, obstructed by keratotic material, could be seen on the forehead, cheeks and ears. No inflammatory signs, either exudation or atrophy, were reported. No subjective complaints were registered. Riehl thought that his melanosis was caused by toxic substances ingested with food, probably flour from different plant seeds —Vicia fava for instance, containing Bloch's pigment precursor, dopa, which was used in the production of bread during the war.

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7. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931, pp. 78-80.

8. Weidman, F.: Histologic Protocols, personal communication to the authors (1945).

9. Hollander, A.: Personal communication to the authors.

10. Riehl: Ueber eine eigenartige Melanose, Wien. klin. Wchnschr. **25**:780, 1917.

Civatte's *poikilodermie réticulée pigmentaire du visage et du cou* was first described by him in 1923.[11] The characteristic feature was a reticular dark brown pigmentation, interspersed with red slightly infiltrated macules and depigmented spots, as well as superficial areas of atrophy. Civatte reported 3 cases in women during the menopause. The dermatosis started slowly, without the subjective symptoms. The first signs were seen on the forehead in the form of red infiltrations, which spread downward to the neck, shoulders, chest and arms. The main changes were on the face, but its median parts, such as the nose and the region around the mouth and eyelids, showed no changes. There was a definite border along the frontal hairline. Therapeutically, Civatte obtained improvement by using organotherapy in the form of adrenal extracts. He first stated the belief that these cases were a variety of Jacobi's poikiloderma vasculare atrophicans, but was finally inclined to classify them as melanodermatitis.

Localized patches, simulating roentgen ray dermatitis and associated with other cutaneous diseases, such as mycosis fungoides, have been labeled poikiloderma vasculare atrophicans, with resulting confusion. The following classification of poikilodermas will serve to emphasize the instability of the disease as a separate clinical entity: (1) poikiloderma vasculare atrophicans (the pure cutaneous type), (2) poikiloderma associated with sclerodermatous changes (scleropoikiloderma) and with dermatomyositis (poikilodermatomyositis) and (3) poikiloderma as the end result or sometimes the beginning of various dermatoses, for example, acrodermatitis atrophicans chronica, lymphoblastoma, leukemia cutis, mycosis fungoides, Hodgkin's disease and arsphenamine dermatitis.

SUMMARY OF CASES IN LITERATURE

It is difficult to summarize the literature and to generalize as to age incidence, causative factors and so forth, because all three of the types listed are described as poikiloderma vasculare atrophicans. It seems that this term should be limited to the pure cutaneous type and that the poikilodermatous changes seen in scleroderma and dermatomyositis and the similar changes seen in the lymphomas should not be called poikilodermavascular atrophicans. The following summary of the literature combines all three types, which are described as "PVA."

Age.—The ages ranged from 6 to 79 years, with an average of 33 years.

Sex.—There was a slightly higher incidence in women than in men.

Occupational Hazards.—The only common denominator among the occupational hazards was exposure to cold, mentioned specifically by

11. Civatte, A.: Poikilodermie réticulée pigmentaire du visage et du cou, Ann. de dermat. et syph. **4**:605, 1923.

Oulmann,[12] and exposure to oily substances containing iron and arsenic. Hazen [13] mentioned a worker in tar. Many of the occupations listed in the literature are those in which there was exposure to physical factors, such as cold and sunlight, as is the case with coachmen, farmers and soldiers and also housewives and cooks, who may dip their hands in cold water.

Previous Treatment.—Cannon and his associates [14] listed 8 cases in which arsenic in the form of arsphenamine or neoarsphenamine was a causative factor. The disease in these cases followed arsphenamine dermatitis. Cannon also reported 2 patients with syphilis who were treated with neoarsphenamine and in whom arsphenamine dermatitis and the classic poikiloderma-like changes developed. One report by Nobl [15] listed "salvarsan" arsphenamine. Whitehouse [16] reported the case of a 13 year old girl who experienced "arsenic dermatitis" and, later, poikiloderma-like changes. LaRocco and Cummer [17] listed a case of poikiloderma vasculare atrophicans following roentgen ray therapy.

Exciting Factors of Exposure.—There are reports of cases in which there was a history of exposure to cold.[18] Zinsser [19] attributed the disease in his patients to injury in early life of the small blood vessels on the most exposed parts of the body. In the cases of Montgomery and O'Leary [20] and of Ingram,[21] cold intensified the erythema. No cases were reported in which exposure to light precipitated the disease or caused exacerbations.

Kindler [22] reported a case of the disease following severe injuries from a motor accident. Many dermatologists have expressed the view

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12. Oulmann, L., in discussion on Taussig.[31b]

13. Hazen, H. H., in discussion on Lane.[4]

14. Cannon, A. B.; Karelitz-Karry, M. B., and Fischer, J. K.: Poikiloderma-Like Changes in the Skin Following Arsphenamine Dermatitis: Report of Two Cases, J. A. M. A. **118**:122 (Jan. 10) 1942.

15. Nobl, G.: Salvarsanbedingte Poikilodermien, Wien. med. Wchnschr. **85**: 1050, 1935.

16. Whitehouse: Poikiloderma, Arch. Dermat. & Syph. **10**:651 (Nov.) 1924.

17. LaRocco, C. G., and Cummer, C. L.: Poikiloderma Atrophicans Vasculare (?), Arch. Dermat. & Syph. **20**:142 (July) 1929.

18. (*a*) Bettman: Ueber die Poikilodermia atrophicans vascularis, Arch. f. Dermat. u. Syph. **129**:101, 1921. (*b*) Bowman, K. M., and Clark, E. C.: A Case of Poikiloderma Atrophicans Vasculare, Arch. Dermat. & Syph. **15**:583 (May) 1927.

19. Zinsser, in Neisser, A., and Jacobi, E.: Ikonographica dermatologica, Berlin, Urban & Schwarzenberg, 1910, pt. 5, p. 219.

20. Montgomery, H., and O'Leary, P. A.: Poikiloderma Atrophicans Vasculare (Jacobi)? Arch. Dermat. & Syph. **25**:942 (May) 1932.

21. Ingram, J. T.: Dermatomyositis and Poikilodermia, Brit. J. Dermat. **46**: 53, 1934.

22. Kindler, T.: Poikiloderma Atrophicans Vasculare, Proc. Roy. Soc. Med **36**:619, 1943.

that the cutaneous picture of poikiloderma vasculare atrophicans might well be the end result of repeated insults to the skin from various factors.[23]

Symptoms.—Pruritus, slight to intense, may be present in the early stages of the disease. Cyanosis of the extremities on exposure to cold was reported in a few papers, usually in cases with associated sclerodactylia.[24] Arthralgia, muscle pains and weakness were noted in patients with muscular atrophy, the so-called poikilodermatomyositis.[25]

Duration.—The duration of the disease was from three months to thirty-eight years.

Cause of Death.—There were reports of 2 fatal cases, in which postmortem examination gave no clue to the cause of death.[26] The other deaths were due to Hodgkin's disease or mycosis fungoides.[27]

Physical Examination.—The general examination revealed nothing unusual except in the patients with muscular atrophy and tenderness (poikilodermatomyositis) or with sclerodactylia and in the case described by Carleton.[28]

Carleton published a paper describing a case that was stated to be poikiloderma vasculare atrophicans, associated with cataracts (Rothmund's syndrome). Scleropoikiloderma has been mentioned as one

23. Oliver, E. A.: Mycosis Fungoides with Poikiloderma-Like Symptoms, Arch. Dermat. & Syph. **33**:267 (Feb.) 1936.

24. (*a*) Schmidt: Zentralbl. f. Haut- u. Geschlechtskr. **17**:45, 1925. (*b*) Rottmann, H. G.: Ueber Poikiloderma atrophicans vascularis (Jacobi) mit bemerkenswerten Nebenbefunden, Arch. f. Dermat. u. Syph. **153**:747, 1927. (*c*) Jaffé, K.: Zwei Fälle von Sklero-Poikilodermie, ibid. **159**:257, 1930. (*d*) Cross, A. G.: Case of Poikiloderma of Jacobi with Complications, Lancet **2**:1104, 1934.

25. (*a*) Petges and Cléjat.[1] (*b*) Oulmann.[12] (*c*) Cross.[24d] (*d*) Petges and others: Bull Soc. franç. de dermat. et syph. **36**:817 and 871, 1929. (*e*) Petges, G., and Petges, A.: Poïkilodermatomyosite dans la jeunesse et l'enfance, Ann. de dermat. et syph. **1**:441, 1930. (*f*) Nicolau, M. S.: Poikilodermia avec atrophies et scleroses muscularies multiples, type Petges-Clijat (Poikilodermie myopathique), Bull. Soc. franç. de dermat. et syph. (Reunion de Strasbourg) **36**:823, 1929. (*g*) Ulitzka, F.: Poikilodermia atrophicans vascularis (Jakobi), Dermat. Ztschr. **54**:119, 1928. (*h*) Horn, R. C., Jr.: Poikilodermatomyositis: Report of a Case with Complete Postmortem Examination, Arch. Dermat. & Syph. **44**:1086 (Dec.) 1941. (*i*) Bruck: Dermat. Wchnschr. **68**:369, 1919. (*j*) Fox, H.: Poikiloderma Atrophicans Vasculare and Lymphoblastoma, Arch. Dermat. & Syph. **35**:549 (March) 1937. (*k*) Usher, B.: Poikiloderma Vascular Atrophicans: Report of a Case, ibid. **25**:683 (April) 1932.

26. Bowman and Clark.[18b] Horn.[25h]

27. (*a*) Oliver.[23] (*b*) Lane, J. E.: Poikiloderma, Arch. Dermat. & Syph. **16**:117 (July) 1927. (*c*) Ormsby, O. S.: Case for Diagnosis, J. Cutan. Dis. **35**:42, 1917.

28. Carleton, A.: Skin Disease and Cataract, Brit. J. Dermat. **55**:83, 1943.

of the characteristics of Werner's syndrome. However, Thannhauser [29] stated the belief that the cutaneous changes are different in their features in both syndromes. In Werner's syndrome the most striking feature is tightening of the skin over the underlying structures, with a paucity of subcutaneous fat tissue. Ulcers develop mainly on the points of pressure on the heels and toes, over the ankles and especially over the achilles tendon. The classification of these cutaneous diseases in the literature as "scleroderma" or "scleropoikiloderma" does not correspond to the clinical or histologic observations. In Rothmund's syndrome the cutaneous lesions are in evidence five months after birth. In contrast to Werner's syndrome, there is no stretching of the skin and no ulcers are present. Because of the recessive heredofamilial occurrence of this syndrome, it is suggested that the cutaneous changes, like the other symptoms of Werner's syndrome, are the result of a defective germ plasm, which does not manifest itself until the second or third decade of life. The designation of the cutaneous changes by a purely descriptive name, such as "heredofamilial atrophic dermatosis with cutaneous ulcers," seem more appropriate. The cutaneous changes of Rothmund's syndrome are classified in the literature as "poikiloderma" or "scleropoikiloderma." Such a classification is not in accord with the heredofamilial occurrence of the cutaneous changes nor with the histologic observations. In conformity with the designation of the cutaneous changes in Werner's syndrome, it also seems appropriate to use for these changes in Rothmund's syndrome a simple descriptive name such as "heredofamilial atrophic dermatosis with telangiectasia."

Distribution: The areas of distribution listed here are based on a tabulation of the literature.

Scalp. Alopecia was rare. "PVA" lesions were present in only 2 cases.

Face. In most cases the face, including the ears, eyelids (occasional transitory edema), forehead and nose, was spared.

Trunk. The lesions occurred in the back, chest, abdomen, buttocks and particularly the anterior axillary folds and in a few cases in the axillas. In 1 case there was decided distribution around the waist line, under the belt.

Extremities. The lesions were observed with equal frequency in the upper and lower extremities, with a predilection for the flexure aspects (elbow and knee). In only 1 case was the palm involved.

Mucous membrane. There were two or three reports of leukoplakia, "white reticulation," on the inner aspect of the cheek.

Symmetry: The distribution was symmetric in all but 1 case.

29. Thannhauser, S. J.: Werner's and Rothmund's Syndrome, Ann. Int. Med. **23**:559, 1945.

Evolution: Gougerot [30] stressed the early lichenoid papule or red patch, the size of a millet seed, as the primary lesion and stated that the disease was slowly progressive. In 1 case the patches were present for eighteen years. No other authors mentioned the evolution of the lesion.

Description: The lesions [31] presented a variegated pattern, consisting of an admixture of telangiectasia, atrophy, hyperpigmentation, depigmentation, miliary lichenoid papules and capillary hemorrhages, the whole being covered with fine furfuraceous scales. The color varied from pale pink through dark brown to livid or rose red, depending on the number of areas of telangiectasia. As the areas were set more closely together, the color became deeper. Characteristically, there were islands of atrophic spots, surrounded by a hyperemic pigmented network, by dark pigmentation and partly by bright red to livid marbling, with numerous areas of telangiectasia and capillary hemorrhages. The hair follicles appeared as darkly limited red brown spots, the size of a pinhead. Ulcers or scars of ulcers were seen.

Laboratory Examination.—Studies of the chemical composition of the blood revealed the nonprotein nitrogen to be normal. The total protein was elevated in 1 case. There was a low level of vitamin C. Creatinuria was observed in cases with involvement of the muscles. Hematologic studies revealed nothing abnormal. Wassermann reactions were negative, and the urine was normal. Roentgenologic examination revealed subcutaneous calcification in several cases.

REPORT OF A CASE

A 67 year old retired construction worker, of Lithuanian extraction, was admitted to the Boston City Hospital on Jan. 18, 1944, with the chief complaint of progressive scaling and itching, of six months' duration.

The patient had been in good health until six years previous to admission, when cellulitis developed following a cut on the finger. In July 1943, after repeated swims in salt water and prolonged sun baths, the patient noticed an

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30. Gougerot, H., and Eliascheff, O.: La petite papule rouge, lesion élémentaire et initial de la poikilodermia reticuleuse de Petges-Jacobi, Arch. dermat.-syph. de la clin. de l'Hôp. Saint-Louis **1**:137, 1929.

31. (*a*) Dowling, G. B., and Freudenthal, W.: Dermatomyositis and Poikilodermia Atrophicans Vascularis: A Clinical and Histological Comparison, Brit. J. Dermat. **50**:519, 1939. (*b*) Taussig, L.: Poikiloderma Atrophicans Vasculare, Jacobi: Report of a Case with a Review of Recent Literature, Arch. Dermat. & Syph. **25**:882 (May) 1932. (*c*) Parounagian, M. B.: Poikiloderma Atrophicans Vasculare, ibid. **29**:915 (June) 1934. (*d*) Hazel, O. G.: Poikiloderma Atrophicans Vasculare: Report of a Case, ibid. **40**:776 (Nov.) 1939. (*e*) Bechet, P. E.: Poikiloderma Atrophicans Vasculare, ibid. **29**:462 (March) 1934. (*f*) Perlstein, M. O.: Poikiloderma Atrophicans Vasculare, ibid. **29**:158 (Jan.) 1934. (*g*) Photinos, P. B.: Contributions to the Clinical Symptoms and Histology of Poikilodermia of Petges-Jacobi, Dermat. Wchnschr. **93**:1461, 1931. (*h*) Counter, C. E.: Poikiloderma Atrophicans Vasculare, Arch. Dermat. & Syph. **49**:85 (Jan.) 1944.

area of bluish discoloration, approximately 3.5 cm. in diameter, on the dorsal aspect of his right wrist. The skin in this area appeared to be coarser than the surrounding skin and was covered by fine silvery branlike scales, associated with itching and a papular eruption. By the following month the lesion had spread by continuity to involve the entire right arm and hand, with the exception of the palm and the elbow. The itching became severer and was worse at night. There were no symptoms associated with any other systems. During this period and throughout September the patient took sun baths in the nude for six to eight hours daily. He noticed no change in pigmentation in the affected areas other than tanning. The eruption spread to involve the neck, back, lower extremities, abdomen, chest and left arm and lastly the scalp and face. The elbows, palmar and plantar surfaces, and genitals were spared. The right upper eyelid was also involved.

Between October 1943 and January 1944, the skin became dry, atrophic and finely pleated, presenting a cigaret paper appearance. Two weeks before admission there was painless bleeding from the lesions, due partly to scratching and partly to fissuring.

The family and occupational histories were noncontributory. There were no other subjective symptoms besides these of the skin. The appetite was excellent, and the diet was adequate.

Physical examination revealed a robust, well developed, and well nourished man, in no apparent distress; except for the skin there were essentially no abnormalities. The entire cutaneous surface had such a peculiar color that the patient's race was undeterminable at first glance. The outstanding features were the reticulated appearance, the pleating, most evident at the flexural folds, and the dry adherent furfuraceous scaling of the entire surface, with pinhead-sized ecchymoses and brilliant red patches. The skin was freely movable throughout and showed no evidence of sclerosis. The color varied from a light yellowish white to a dark dirty brown. The light areas were atrophic and tended to be circular, smooth and surrounded by a dark reddish or purple border; some were confluent and others discrete. The scalp was bald at the vertex and sparsely haired in the parietal and occipital areas. The skin of the scalp was covered with light atrophic circular patches, 1 to 1.5 cm. in diameter and surrounded by deeply pigmented areas. The forehead and cheeks, especially in the malar area, were deeply pigmented and almost blackish brown. The eyelids, especially the right one, were edematous and deeply pigmented. The ears were atrophic and reddish pink, especially the upper half; the lower part was pigmented. The body and extremities were fairly well developed, with fairly firm musculature. The nipples were heavily pigmented, and the skin showed varying degrees of pigmentation, with scattered atrophic areas similar to those on the scalp. Over the left clavicle and midsternum there were brilliant red areas, with fine punctate ecchymoses and scattered areas of telangiectasia. Similar areas were present on the inner aspect of the arms. Most of the hair was absent from the follicles, which frequently showed minute hemorrhages. On the posterior aspects of the arms and the chest there were areas of what appeared to be typical roentgen ray dermatitis, brilliant erythema, dryness and thin loosely adherent scaling, with alternating areas of depigmentation, hyperpigmentation and telangiectasia. On the arms were areas of decided pleating, scaling and anetodermia of varying degrees of pigmentation, and capillary hemorrhages. The genitals presented a few lichenoid papules, with crinkling, atrophy and furfuraceous scaling. The appearance of the legs was similar to that of the arms, but the areas of depigmentation were surrounded by red violaceous borders.

The feet were slightly edematous and pigmented, with furrowing of the anterior aspect of the ankles. The veins were not prominent. The infra-red film showed no enlargement of the vessels. There were occasional excoriations on the body and extremities. There were no vesicles or bullae, and none were ever present throughout the patient's illness.

The white cell count was 7,000, with 6 per cent young forms, 46 per cent mature forms, 38 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The nonprotein nitrogen in the plasma was 38 mg. per hundred cubic centimeters, the serum calcium 10.3 mg., the serum phosphorus 4

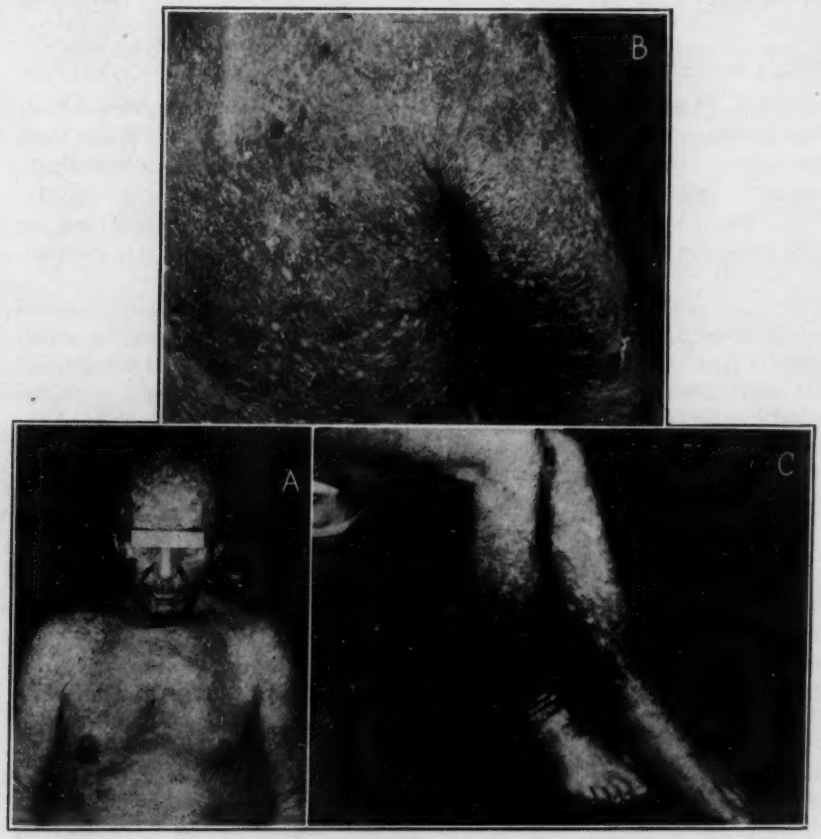

Fig. 1.—*A*, generalized pleating and scaling, with telangiectasia and circular areas of atrophy surrounded by reticulated pigmentation. The dark areas were brilliant red because of capillary dilatation and hemorrhages. *B*, posterior aspect of the chest and arm showing a peculiar clam shell scaling, with atrophy and telangiectasia resembling a roentgen ray burn, and decided pleating. *C*, reddish violaceous lacework pattern on the legs, due to dilated capillaries and increased pigmentation, and edema and scaling on the dorsa of the feet, with pleating at the anterior aspect of the ankles.

mg. and the serum phosphatase 4.3 Bodansky units. The corrected sedimentation rate was 19 mm., 16 mm. and 13 mm. per hour. The hematocrit reading was 41.5 per cent, the icteric index 5 units and the prothrombin time 100 per cent. The

vitamin A content of the serum was 95 international units per hundred cubic centimeters of serum and the carotene 52 micrograms. The reaction to the cephalin flocculation test was negative. The stools were normal. Roentgenologic examination of the skull revealed it to be normal.

Treatment consisted of starch baths and high vitamin diet. There was no change except for relief of the swelling of the feet and ankles. The patient was discharged on February 23.

The patient was frequently observed in the outpatient department. The skin became less pigmented and the atrophic areas larger. The itching became intense, with resulting increase of the excoriations, so that the patient was rehospitalized

Fig. 2.—The patient as he appeared one week before death, when he presented numerous areas of denuded skin which continued to ooze serous and bloody discharge without crusting. The atrophic and hemorrhagic areas became enlarged and the skin more glossy and less scaly.

on September 11. Increased vascular permeability was noted by the fact that the excoriations did not crust, but continued to ooze serum and later a bloody discharge. Hemorrhagic areas became prominent, and shortly before death large patches of the skin remained denuded and bloody (fig. 2). The bleeding was so excessive that pressure bandages were required and used until death, which occurred on Jan. 9, 1945.

Observations at Autopsy.—Autopsy was performed twelve hours post mortem. The report was as follows:

Gross Observations: The body was that of a well developed cachectic-appearing white man of about 65 years. There was an offensive odor to the body, and practically the entire skin was involved in an abnormal process. The skin of the right thigh was thin and parchment-like and had scattered purple-red areas. On the legs there were scaling and dryness of the skin On the left foot, mesially and anteriorly, there was loss of epidermis and subcutaneous tissue, the result of a recent burn. The chest, back and abdomen revealed loss of the surface layers of the skin, with a moist layer visible. There were numerous foci that were infected and foul smelling, and the skin in many places was covered with so-called triple dye.

The pupils were equal in diameter, and the hair of the scalp was sparse. There was no jaundice or pitting edema of the lower extremities.

The peritoneal cavity contained old adhesions, which coursed from the omentum to the anterior parietal peritoneum. The appendix appeared normal. The stomach and small intestine were moderately distended. The edge of the liver was 2 cm. below the right costal margin. The right pleural space contained old adhesions, laterally and posteriorly. The left pleural space was normal.

The pericardial cavity contained 15 to 20 cc. of straw-colored fluid; there were no adhesions. The heart weighed 375 Gm. The left ventricle was dilated, and the myocardium was unusually flabby and brown-yellow. Otherwise, the heart was essentially normal. The right lung weighed 860 Gm. and the left lung 740 Gm. The bronchi were injected, and the right main bronchus contained friable material, apparently aspirated. The cut surface of the lungs revealed dark red unusually moist parenchyma, with no areas of consolidation. The spleen weighed 400 Gm., and the capsule was smooth. The cut surface was pink-red and soft, and the follicles were indistinct. The liver weighed 2,100 Gm., and the capsule was smooth. The cut surface was pale brown, with indistinct vascular markings. The kidneys weighed 340 Gm. The capsules stripped with some difficulty from smooth surfaces. The cut surface was red-brown, with a well demarcated cortex. The pelves and ureters appeared normal. The aorta was smooth and elastic, with minimal arteriosclerotic involvement. The remainder of the gross autopsy observations, essentially, were not unusual.

Bacteriologic Study: The right lung contained Clostridium welchii, Escherichia coli and Proteus vulgaris and the left lung C. welchii and P. vulgaris.

Microscopic Study: Sections were fixed in Zenker's fluid and stained with phloxine-methylene blue.

Heart: The myocardium showed localized collections of interstitial leukocytes, with a few polymorphonuclear cells and in places numerous lymphocytes. The muscle bundles showed no change.

Lungs: In the pulmonary vessels there was rather decided thickening of the walls. The alveolar spaces contained amorphous granular material. Numerous large mononuclear cells were noted at times, adjacent to plump rod-shaped organisms. In numerous alveolar spaces there were mononuclear cells, granular debris, with occasional black granular material, and shadows of what appeared to be red blood cells.

Liver: There were focal accumulations of lymphocytes, with fibrosis in one small area close to such a collection of cells.

Kidney: The capsule was slightly thickened, and there were numerous focal collections of lymphocytes replacing glomeruli and tubules. In places there was fibrosis of the parenchyma, with scattered lymphocytes nearby, as well as dilated tubules containing amorphous purple-staining casts. The interstitial tissue was

infiltrated in an irregular fashion, with small collections of lymphocytes. The tubules appeared widely separated by a collection of amorphous material, which seemed to separate the fibrillar strands of the interstitium. The glomeruli showed varying degrees of increase in the thickness of basement membranes, with minimal pericapsular fibrosis. The arterioles presented moderate reduction in the width of the lumens.

The microscopic sections of the other organs were essentially normal.

Skin (right thigh): The epidermis appeared thinned, particularly the prickle cell layer; the intercytoplasmic processes stood out prominently. The epidermis appeared flattened, and the rete cones were not prominent. Beneath the stratum

Fig. 3.—Section of skin from the abdomen, showing hyperkeratosis, loss of prominence of rete pegs, inflammatory infiltrate and numerous distended and thickened blood vessels. × 80.

germinativum were numerous foci of lymphocytes infiltrating the pars papillaris of the cutis and prominent capillaries, which were distended. Granules of yellow-brown pigment stood out in cells of the papillaris area of the cutis (fig. 3 and 4).

Abdomen: The outstanding changes were the presence of dense foci of lymphocytes, with an occasional plasma cell in the pars papillaris, immediately below the epidermis. There was no border zone of connective tissue separating the inflammatory infiltrate from the epidermis. The cutaneous appendages, such as sweat glands and hair follicles, showed no significant changes The epidermis was

somewhat thinned, and the rete cones were not prominent. In the large vessels there was moderate to advanced thickening of the walls, apparently mainly a thickening of the mediums.

Elsewhere in the section there were numerous polymorphonuclear leukocytes infiltrating the pars reticularis and extending into the pars papillaris. Many lymphocytes were also present in the pars reticularis.

Special stains. Sections were fixed in Zenker's fluid and stained for iron by Gomori's method and for elastic tissue by the Verhoeff method. Sections from

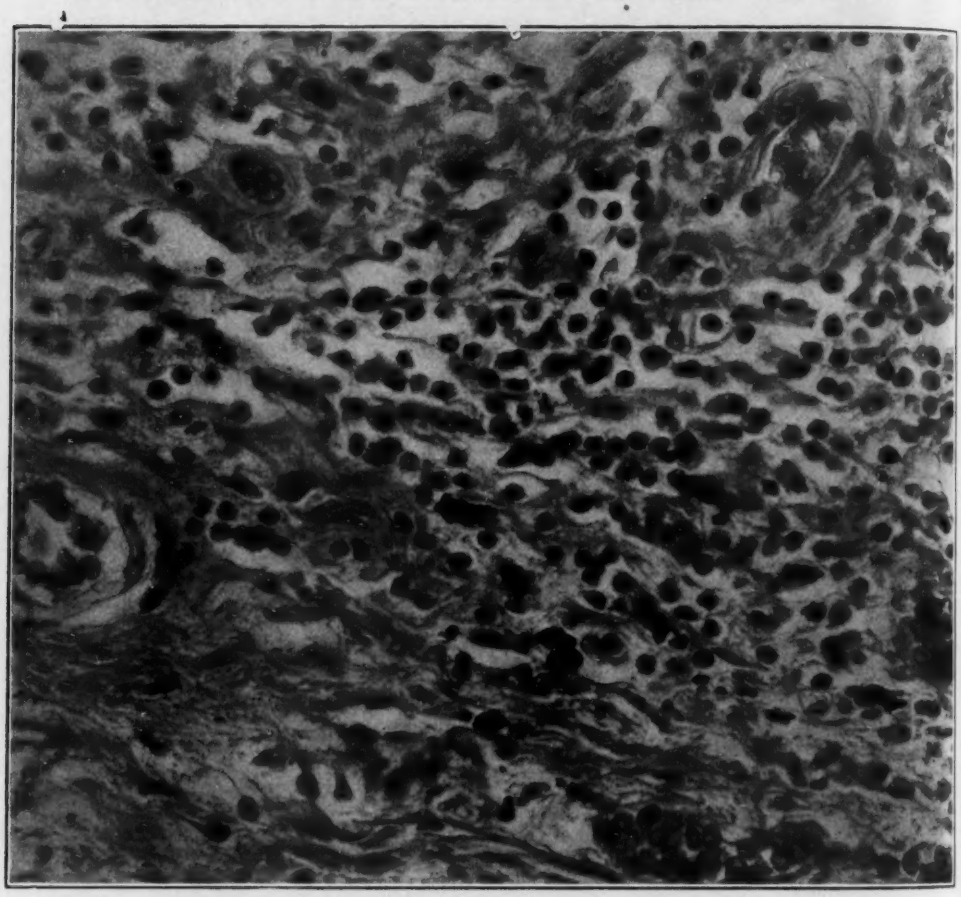

Fig. 4.—Section of skin from the right thigh, showing inflammatory infiltrate, chromatophores and prominent blood vessels. × 650.

the thigh and abdomen stained for iron failed to reveal the presence of iron pigment in the chromatophores, situated mainly in the pars papillaris of the cutis. Sections from the same sites stained for elastic tissue revealed almost complete loss of the tunica elastica in the cutis where the inflammatory infiltrate was noted.

Striated muscle. There were no significant changes. In the smaller blood vessels there were minimal thickening of the walls. No inflammatory infiltrate of cells was noted.

Fat and muscles. No changes were noted except for the fact that the muscle bundles appeared to be abnormally spread apart by amorphous pink-staining material.

Anatomic Diagnoses.—The anatomic diagnoses were as follows: poikiloderma vasculare atrophicans, with superimposed infection, interstitial myocarditis, dilatation of the right and left ventricles of the heart, benign nephrosclerosis and old pleurisy (right pleura).

CLINICAL COMMENT

This case, both clinically and pathologically, was truly one of a cutaneous disease presenting all the cardinal signs of the entity termed poikiloderma vasculare atrophicans. Death resulted from cutaneous toxemia. At no time did the patient have vesicles, bullae, infiltrated patches, tumors of the skin or lymphadenopathy, and the symptoms from beginning to end were cutaneous. Apparently there are cases in which poikiloderma vasculare atrophicans is an independent disease that terminates fatally. Perhaps there was an underlying cause of death in this case, but autopsy failed to reveal it. The patient had a vascular permeability, as evidenced by profuse oozing of serum. He showed no evidence of an endocrine dystrophy. During the last observation in the outpatient department, although the entire skin was affected, he did not complain of weakness or especial fatigue. The chief symptom was intense itching. It was certainly not due to embryonic defect, for the patient had no symptoms until late in life.

The only possible causative factor in this case was excessive exposure to sunlight. For the entire summer the patient frequented an enclosed bathing beach where men exposed themselves to the sun for many hours at a time. This could have been the precipitating factor in the production of the cutaneous changes. One of us (J.G.D.) has frequently visited this beach, and since observation of this patient he has examined the skin of many of the older habitués who expose their skin for several hours daily. He has noted, particularly on the legs, typical poikiloderma-like changes. In blond persons this has been noticeable on the legs, face upper part of the back, and chest. Some of these men have been frequenting the beach for as long as thirty or forty years. Practically all the older men showed some type of actinic dermatosis, hyperpigmentation, atrophy and numerous areas of telangiectasia, with scattered senile keratoses on the areas previously mentioned.

When this patient was first seen, the atrophy and pigmentation were the outstanding factors, and it was decided that the case was one of atrophia cutis idiopathica, but the brilliant red areas suggested poikiloderma vasculare atrophicans. The progress of the disease confirmed this diagnosis.

After reading Oliver's excellent review,[23] we decided to continue observation of this case in order to determine whether the patient later experienced signs of mycosis fungoides. Continued observations and

studies of the blood revealed no evidence of infiltration of the skin or blood dyscrasias and no evidence of Hodgkin's disease, the terminal ending in Lane's famous case.[27b] Lymphosarcoma, the terminal disease of Ormsby's patient,[27c] should have been revealed at autopsy. There was no evidence of sclerosis or of myositis, as described by Petges and Cléjat.[1] At no time did this patient receive roentgen ray therapy. He never showed any sign of sclerosis, and the veins were not prominent, which rules out the possibility of association with scleroderma or acrodermatitis chronica atrophicans.

If one keeps in mind the picture of a patient suffering from an intense itch, but no other subjective symptoms, with scaly pleated skin, showing atrophic patches surrounded by reddish pigmented network, shining punctate hemorrhages and telangiectasia, there should be no difficulty in classifying this case as one of poikiloderma vasculare atrophicans, especially since the histologic picture presents the characteristics herein described.

HISTOLOGIC STUDIES

Poikiloderma vasculare atrophicans of Jacobi, listed under the diseases with cutaneous atrophy,[32] is characterized by widespread telangiectasia, pigmentation and cutaneous atrophy. This report presents a case that at autopsy had been diagnosed clinically as poikiloderma vasculare atrophicans. The following histologic changes were evident: thinning and flattening of the epidermis, loss of prominence of the rete pegs, increased deposition of pigment in chromatophores in the region immediately beneath the flattened epidermis (iron stains showed this pigment not to be iron), subpapillary lymphocytic foci and vascular dilatation and prominence in the pars papillaris of the cutis. Further studies revealed decided loss of elastic tissue in the region of the cutis, where the inflammatory infiltrate was most dense. The striated muscle showed no changes, and the fat appeared normal. However, it appeared that the muscle bundles were spread apart by amorphous pink-staining material (edema of the tissues). It is believed that the histologic features of this case are consistent with the clinical diagnosis of poikiloderma vasculare atrophicans, and the histologic changes in the skin are similar to those described in other papers.

In addition to this case, we were recently permitted to review some of the microscopic sections of Montgomery and Sullivan and the histologic protocols and microscopic sections of Weidman,[8] as well as slides from the Army Medical Museum.

In Lane's [4] résumé of the nature of this disease, he stated that two stages are noted. In the first stage, there are perivascular infiltration of round cells and dilatation of the superficial vessels, with alternate increase and diminution or absence of pigment. In the second stage,

32. Ormsby, O. S.: Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1937, p. 586.

the papillae are flattened and there are degeneration and disappearance of the elastin and atrophy of the collagen bundles. Early cases of poikiloderma vasculare atrophicans may show sharply localized areas of atrophy and condensation of the epidermis. In the corium the only pathologic change consists of a slight perivascular round cell infiltration at the level of the subpapillary plexus of vessels. The cells are mostly lymphocytes. Such changes are unassociated with edema, either in the corium or in the papillae. Other reports have emphasized the atrophy of the epidermis, the destruction of the basement membrane as a result of the extension of the round cell infiltrate from the corium well into the epidermis, severe edema of the papillary and subpapillary areas, hyperplasia of arterioles and cellular infiltrate in the corium, diffuse in distribution.

Diseases that have frequently been considered in the differential diagnosis are acrodermatitis chronica atrophicans, disseminated lupus erythematosus, dermatomyositis and scleroderma. It is thought that the histologic features of the case herein reported differ from those about to be presented and that therefore poikiloderma vasculare atrophicans can be differentiated from other cutaneous diseases with which it is often confused.

Montgomery and Sullivan [6] expressed the belief that the histologic changes in acrodermatitis chronica atrophicans are diagnostic in practically all cases if a specimen for biopsy is taken from a well developed region, independent of any associated fibrous nodules, sclerodermatous changes or ulcers. The following combination of changes makes a diagnostic picture: relative to absolute hyperkeratosis, preservation of a granular layer, atrophy and flattening of the prickle cell layer, loss of rete ridges and papillary bodies, with resultant flattening of the epidermis into a thin wavy line, and a definite grenz or border zone of normal to homogenized connective tissue between the epidermis and the infiltrate in the cutis. Much emphasis is laid by the authors on this zone, which is apparently characteristic of acrodermatitis chronica atrophicans and is not seen in poikiloderma or other diseases. Also, in poikiloderma liquefaction degeneration of the basal cell layer occurs, a change that is not seen in acrodermatitis. Another possible differential point is the presence of chromatophores in poikiloderma, containing a non-iron pigment in the pars papillaris of the cutis, whereas these are not observed in acrodermatitis. Some of the more unusual features of acrodermatitis chronica atrophicans, such as fibrous nodules, arthritis deformans, ulnar bands, scleroderma-like changes and involvement of the mucous membranes, may permit ready differentiation from poikiloderma and other cutaneous diseases.[33]

33. Sweitzer, S. E., and Laymon, C. W.: Acrodermatitis Chronica Atrophicans, Arch. Dermat. & Syph. **31**:196 (Feb.) 1935.

In contrast to poikiloderma and acrodermatitis, the pathologic changes of disseminated lupus erythematosus are frequently distinctive, so that these entities may be separated. However, Montgomery[34] stated that the histologic picture of poikiloderma vasculare atrophicans of Jacobi may simulate the telangiectatic or atrophic changes of disseminated lupus erythematosus. Characteristic pathologic changes in the latter disease consist of relative and absolute hyperkeratosis, keratotic plugging of hair follicles and sweat ducts, preservation or even thickening of the granular layer, acanthosis of the prickle cell layer with adjacent regions of atrophy, liquefaction necrosis of the basal cell layer, dilatation of the superficial capillaries and lymphatics, edematous changes in the cutis and destruction of elastic tissue where the infiltration occurs and the presence of a varying number of chromatophores laden with melanin. In all types of lupus erythematosus, according to Montgomery, there is slight but definite increase in the number of lattice fibers, which to him suggested involvement of the reticuloendothelial system.

Klemperer,[35] on the other hand, emphasized the degenerative phenomena in disseminated lupus erythematosus and pointed out that infiltration of inflammatory cells is scant. The earliest change, according to him, is shown as homogenization of the collagen fibrils and ground substance in the most superficial layer of the corium. The ground substance and fibers undergo fibrinoid degeneration as the process advances. The vascular lesion in the skin is evidently determined by involvement of the connective tissue matrix of the corium, which is continuous with the connective tissue of the vessel wall. The degenerative changes in the epidermis are considered secondary to changes in the connective tissue of the corium and its blood vessels. The vascular changes, according to the same author, show as a deposit of homogeneous eosinophilic material within the tunica intima, between muscle fibers, or in the tunica adventitia. A further change is the deposition of rings of fibrinoid material in the tunica intima, choking the lumen. With complete fibrinoid change of the collagenous framework of the vessel wall, destruction of muscular and elastic elements takes place. These changes, described in the blood vessels and in the ground substance of the corium, are not seen in poikiloderma or acrodermatitis.

Dermatomyositis and scleroderma are so commonly confused that these diseases are considered separately and also are compared as to their histologic features. In a case of fatal acute diffuse scleroderma reported by MacCallum,[36] microscopic studies revealed no changes in

34. Montgomery, H.: Pathology of Lupus Erythematosus, J. Invest. Dermat. **2**:343, 1939.

35. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

36. MacCallum, W. G.: Acute Diffuse Scleroderma, Tr. A. Am. Physicians **41**:190, 1926.

the skin. He expressed the belief that the collagen fibers in the corium were possibly slightly more coarse than normal, but otherwise, after careful study, there were no further changes seen. The underlying muscle in this case showed no abnormality. The nature of scleroderma was discussed by Rake [37] in a report of cases which came to autopsy. The outstanding change consisted of a slight degree of thinning of the epidermis, with the dermis occupied by dense scar tissue in the form of interlacing hyaline fibers and containing few cells. This hyaline connective tissue extended in strands into the subdermis between somewhat atrophied fat lobules. There was no sign of inflammation. In the smaller arteries in the dermis there were somewhat thickened walls, due to proliferation of the tunica intima and endothelium, but the lumen was not occluded. The sweat glands were small and atrophic. Elastic tissue stains showed elastic fibers to be plentiful in the connective tissue of the dermis. This feature is contrasted with the absence and destruction of the same tissue in poikiloderma vasculare atrophicans. The arrectores pilorum were hypertrophied and appeared as conspicuous bands. A section of voluntary muscle from the thigh showed shrunken hyaline and dark-staining fibers lying intermingled with fibers that were swollen, pale and apparently disintegrated. The cross striations could be seen in the shrunken fibers, but not in the swollen ones. The nuclei of the sarcolemmas around the former were approximated and appeared as nearly continuous lines; some of these fibers were tortuous and curled.

Turnbull [38] ascribed the changes in the skin in a case of scleroderma to inflammation, and such an interpretation has been adopted by others. In Rake's cases there was nothing that suggested an inflammatory process.

Kinney and Maher,[39] in a report of cases of dermatomyositis that came to autopsy, have described in detail the histologic features of this disease. In the epidermis there were atrophy and evidence of degeneration and in the dermis increased compactness, with the usually loosely woven connective tissue and elastic fibers bound together by fibrous connective tissue, much of which had a hyalinized appearance. Continuous with the dermis and extending into the underlying fat were broad sheets of tissue, which in some places had a densely collagenous character. Other cases reported in this paper presented epidermal atrophy and "balloon" cells, flattening of the papillae, edema of the dermis and an increase in fibrous connective tissue in the dermis, in which inflammatory cells were

37. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931.

38. Turnbull, H. M., cited by Castle, W. F.: The Endocrine Causation of Scleroderma Including Morphoea, Brit. J. Dermat. **35**:255, 1923; cited by Rake.[37]

39. Kinney, T. D., and Maher, M. M.: Dermatomyositis, Am. J. Path. **16**: 561, 1940.

not significant. The authors stated that the lesions of the muscles in dermatomyositis appear to be of sufficient diagnostic import to warrant the separate classification of the two diseases. In many places the muscle fibers had an amorphous appearance, with loss of the usual fibrillar structure. In these areas striations were lost, the fibers had large and small vacuoles, or there was a loss of the sarcolemma nuclei. These changes occurred singly or in combination. There was widespread edema, not only between the muscle bundles but between the individual muscle fibers as well. There were patches of exudate throughout the muscle bundles, composed of small lymphocytes, plasma cells and a rare polymorphonuclear leukocyte. Some of the muscle fibers had been replaced by pale-staining fibrous connective tissue. There was a decided perivascular infiltrate by an exudate similar in character to that seen in the muscle.

Brock,[40] comparing the histologic features of scleroderma and dermatomyositis, pointed out that the inflammatory infiltrate in the former is minimal, whereas the same process in dermatomyositis is a cardinal feature. The parenchymatous degeneration of muscle is varied and diffuse and constitutes a cardinal feature of dermatomyositis, whereas in scleroderma this change is not prominent and is usually proportionate to the interstitial sclerosis. The vascular changes, according to this author, are minimal in dermatomyositis and a cardinal feature in scleroderma. He concluded by stating that the connective tissue changes and sclerosis of scleroderma are distinctive and form another link in the attempt to differentiate the two entities.

CONCLUSIONS

A case is reported, with observations at autopsy, of a man with a cutaneous disturbance consisting of reticulated atrophy, telangiectasia and pigmentation, similar to that termed by Jacobi as poikiloderma vasculare atrophicans. Death resulted from hemorrhage and toxemia of the skin. Autopsy revealed the disease of the skin to be the primary cause of death.

The following histologic changes are distinctive of poikiloderma vasculare atrophicans: thinning and flattening of the epidermis, loss of prominence of the rete pegs, increased deposition of pigment in chromatophores in the region immediately beneath the flattened epidermis (iron stains revealed this pigment not to be iron), subpapillary lymphocytic foci and vascular dilatation and prominence in the pars papillaris of the cutis.

Physical factors, such as exposure to extremes of temperature and actinic radiation, should be considered as precipitating factors in the

40. Brock, W. G.: Dermatomyositis and Diffuse Scleroderma: Differential Diagnosis and Reports of Cases, Arch. Dermat. & Syph. **30**:227 (Aug.) 1934.

onset of this disease. In the present case, the sole causative factor appeared to be overexposure to sunlight. Although localized patches of the dermatologic complex called poikiloderma may occur in other diseases, there is a generalized disease called poikiloderma vasculare atrophicans that is a distinct clinical and histologic entity.

This case proves that not in all patients showing the clinical picture of poikiloderma vasculare atrophicans do symptoms of another disease, such as mycosis fungoides, develop. It emphasizes the importance of recognizing individual clinical entities for the purposes of treatment and prognosis. The mere fact that in some patients presenting poikiloderma or psoriatic lesions a picture of mycosis fungoides later develops does not mean that there is no disease entity that should be labeled poikiloderma vasculare atrophicans or psoriasis.[41]

520 Commonwealth Avenue.

ABSTRACT OF DISCUSSION

DR. STUART C. WAY, San Francisco: I am indebted to Dr. Downing for this opportunity to discuss his interesting and excellent paper. His photographs, too, were fine. From every standpoint, the case appears to represent a typical example of poikiloderma atrophicans vasculare and is, judging from the photographs, one with the most extensive involvement that I have seen.

While Dr. Downing's clinical and microscopic studies tend to establish poikiloderma atrophicans vasculare as an entity, reports of cases by other men present much to be overcome. Regardless of the fact that antemortem and postmortem observations in this case were insufficient to establish the cutaneous changes as secondary to Hodgkin's disease, lymphosarcoma, mycosis fungoides and neurosyphilis, the presence of the changes during the terminal phase of other reported cases cannot be overlooked, as has been brought out by Foerster, Hazel, Jacob and others. Although the dermal pathologic changes did not appear to be secondary to or associated with a primary cause, such a possibility did exist, however undiscoverable it may have been.

I do not recall whether the brain tissues were examined at the time of the autopsy. This is a necessary procedure, however, as there is reason to believe that dermal pathologic changes may be due to degenerative changes of the central nervous system.

Until several days ago it was my impression that the various reported cases, especially the recent case of Kalz and Hoogstraten, had practically stabilized the status of poikiloderma atrophicans vasculare as a cutaneous symptom of a number of known and unknown diseases and had removed it from the clinical entities.

These authors described a case of the Jacobi type, associated with meningovascular neurosyphilis, in which the cutaneous manifestations completely responded to bismuth compound, arsenic and hyperpyrexia therapy.

It is difficult to evaluate the part played by the fever therapy, although I have observed that scleroderma, a disease in some respects not unlike poikiloderma atrophicans vasculare, occasionally shows some response to localized heat, especially infra-red.

41. Dr. F. Parker Jr. contributed to the preparation of this paper.

Past reports of cases emphasize the necessity for examining patients with poikiloderma atrophicans vasculare from a neurologic, endocrinologic, hematologic and vascular standpoint.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I enjoyed Dr. Downing's paper. I have been working with Dr. Helen J. Hare on a group of some 20 cases of poikiloderma, possibly 3 of which would be regarded as of the idiopathic type. Jacobi's original case was that of a farmer who had atrophy of the shoulder muscles and drooping of the head, which suggest strongly that his case was one of poikilodermatomyositis. Petges reported cases of poikilodermatomyositis, but he still differentiated Jacobi's case from his own. Oppenheim in his discussion of Cannon's paper expressed the thought that Petges' cases and Jacobi's case were similar.

Dr. O'Leary and other members of our department have seen a number of cases of dermatomyositis with poikiloderma-like changes. The cases of poikiloderma vasculare atrophicans which have been reported in this country by Lane, Ormsby, Oliver and others have been cases that have eventuated in mycosis fungoides or lymphoblastoma. I have seen 7 such cases. Dr. Ormsby and Dr. Otto Foerster were hesitant to accept as poikiloderma of Jacobi a case that I presented with Dr. O'Leary in 1932, at a meeting of the Chicago Dermatological Society, because the man in this case showed some changes suggesting a pituitary disturbance. That man was seen later by Dr. Osborne, at which time mycosis fungoides had developed. He died about ten years later of lymphosarcoma.

Extensive poikiloderma may also be seen in patients with endocrine disturbances, as illustrated by the disease in a child whom I saw recently with so-called Rothmund syndrome. (A slide was shown.) There was deformity of the bones of the hand, but no evidence of dermatomyositis. The disease started at 3 years of age. I have seen several cases of poikiloderma as an end stage of subacute disseminate lupus erythematosus. I had 1 case of localized traumatic poikiloderma, similar to the second case that Dr. Downing reported.

I reported with Dr. R. R. Sullivan a case of extensive poikiloderma in association with acrodermatitis chronica atrophicans in a patient who had previously been presented by Dr. Graham before the New York Dermatological Society (ARCH. DERMAT. & SYPH. **51**:32-46 [Jan.] 1945). In other words, poikiloderma vasculare atrophicans may represent a syndrome and not a disease entity. On the other hand, just before coming to the meeting, I saw a man aged 73 who had a classic picture of poikiloderma and who gave a history of having had the disease for forty years, without progression and without ever having had treatment of any sort. His general examination did not reveal any abnormalities. There were 2 other cases in which the disease was of shorter duration and in which we were unable to demonstrate any other cutaneous or systemic disease.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I have been particularly interested in Jacobi's poikiloderma vasculare atrophicans since 1920. At that time I saw in an old edition of "Ikonographia dermatologia" what I thought was a classic case, and since then I have been particularly interested. I can say offhand that while one sees many poikiloderma-like changes, one seldom sees a typical picture. At least, to my eye they are not typical; they are not even strongly suggestive.

It is often stated that this type of poikiloderma resembles radiodermatitis or actinic dermatitis. I cannot see the close resemblance except in exceptional cases. Only occasionally does one see old radiodermatitis which at all resembles poikiloderma of Jacobi. These poikiloderma-like changes, of course, are seen in some patients with Riehl's melanosis and some types of lupus erythematosus disseminatus, and are occasionally seen in lymphoblastoma and such diseases, but I cannot see that they closely resemble the true Jacobi type of poikiloderma.

Montgomery's note on his recent case of thirty years' duration, while I did not see the patient, suggested to me the possibility of a typical case of the Jacobi type. Since I have followed this cutaneous picture with much interest, I discussed the situation with Gans repeatedly, but he was rather noncommittal. In 1930 I had the chance to visit with Professor Jadassohn for some time, and naturally we discussed many borderline problems, including poikiloderma. He had seen the originally reported case and readily said that it had nothing to do with lupus erythematosus, although when it was first presented he had favored that diagnosis. He also readily admitted that it was a typical picture, and as we went along he said, "I will show you," and he showed me a typical picture.

I cannot see that this picture in any way resembles that with the common poikiloderma-like changes, if a critical attitude is taken, and I think that for the purposes of scientific study we should be more critical of the picture as seen in the skin. I have seen only 2 patients with the disease, plus 1 in Europe, and I lean to the opinion that these patients have a congenital anomaly of some type in which the cutaneous manifestations are probably brought out, as in Dr. Downing's patient, by some irritation. Without that, the anomaly might not be manifest for many years.

Maybe it would be better if it were called a biologic inferiority rather than a congenital anomaly, but I do not believe that this picture, if it is followed critically, is distinct. Rothmund's syndrome on the skin does not in any way suggest it. Because of the diagnostic acumen of Dr. Paul Anderson, I saw a typical case in Los Angeles, but the picture of poikiloderma of Jacobi, to me, was not suggested for a moment.

I was glad to hear Dr. Downing take the point of view that he did, but I would like to feel that one should be more critical in interpreting the morphologic picture as is seen on the skin. It must be rare, because I have followed it in the meetings and elsewhere with much interest and have seen only 2 cases that I would place in that category from a purely morphologic standpoint.

Dr. Frederick R. Schmidt, Chicago: I enjoyed Dr. Downing's presentation, particularly his statement that we have been disappointed in our observations at autopsy in cases of cutaneous disease. I think that one should look to living tissue for the explanation of some of these changes in the skin. A man who has a coronary disease and who has had an attack and has survived is warned by his physician to avoid three things particularly: emotion, exertion and cold. Why? Because these three things release epinephrine. Epinephrine works as a vasoconstrictor on the coronary vessels and produces the anoxia which is the cause of the cardiac failure.

This pertains to the physiology of the skin in the same way. When cold is applied to the skin, there is an immediate response and histamine is produced with vasoconstriction and subsequent vasodilatation. This vascular reaction is irreversible. It cannot be reversed and still leave a normal blood vessel.

The same thing pertains to lupus erythematosus with respect to sunlight. After exposure to sunlight, there is damage done to the blood vessels, which process is again irreversible. Not only is histamine produced, but there are certain vitamins in the skin, water-soluble vitamins, such as riboflavin, which are destroyed by sunlight, and that process cannot be reversed. Therefore, I heartily subscribe to the premise in Dr. Downing's interesting paper that external factors, such as cold, play a role in the case of housewives and other persons who are repeatedly exposed to cold, whose skin may be damaged irreparably, as in the case after exposure to sunlight.

DR. JOHN GODWIN DOWNING, Boston: I wish to thank all the discussers. In answer to Dr. Way, I wish to say that this man never showed any signs of syphilis. His history and clinical and laboratory examinations revealed no abnormalities. I visited this man frequently in order to keep him contented at the hospital—he was an interesting and intelligent conversationalist. Unfortunately, my colleagues and I were unable to get permission to examine the brain.

In order to emphasize another physical factor in the precipitation of this disease, I would like to show three slides illustrating successive stages of another case of poikiloderma vasculare atrophicans. They picture a 48 year old man who was an iceman for twenty-eight years. He usually carried the ice on his left shoulder. In the process of loading it, he placed the load on the anterior aspect of the upper third of either thigh and on the iliac crest and then lifted it to the shoulder, usually the left. These slides show colored photographs of areas of poikiloderma, corresponding to the sites of greatest contact with the ice. I plan to publish a report of this case later.

SIMPLE PLASTIC MOUNT FOR PERMANENT PRESERVATION OF FUNGI AND SMALL ARTHROPODS

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WE HAVE employed with success, as a medium for the mounting and clearing of biologic specimens, a recently synthesized resin, or plastic, polyvinyl alcohol, known commercially as "PVA."[1] This substance when combined with lactic acid and phenol provides a permanent hyaline mount and also clears and dehydrates the specimen in a satisfactory manner. The latter features are especially advantageous when it is desired to preserve for teaching purposes or for study collections such biologic forms as the scabies mite, ticks, fleas and lice or their ova. In the preservation of cutaneous fungi, the method is adaptable to material removed from ordinary cultures of fungi, actively growing slide cultures and material in the form of scrapings of skin for the purpose of direct microscopic study.

Polyvinyl alcohol was first employed in biologic work by Lubkin and Carsten[2] as a medium for the elimination of dehydration in the preparation of tissues by histologic technic. More recently Downs[3] reported in detail on its use in the preservation of mosquitoes and their larvae, Giemsa-stained blood films, trematode cercariae, motile micro-organisms and pollen grains.

Polyvinyl alcohol is a white powder, or amorphous granular substance, which is soluble or dispersible in water. The aqueous solution is clear and syrupy in consistency, and the viscosity of the solution may be varied by the amount of water added. Films prepared from this substance are resistant to ether, xylol and acetone. We have prepared

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1. "PVA" (Grade RH-349), a synthetic polymer of vinyl alcohol, is available through the E. I. du Pont de Nemours Company, R. & H. Chemical Department, Niagara Falls, New York, at a cost of approximately $1 per pound.

2. Lubkin, V., and Carsten, M.: Elimination of Dehydration in Histological Technique, Science **95**:2477 (June 19) 1942.

3. Downs, W. G.: Polyvinyl Alcohol: A Medium for Mounting and Clearing Biological Specimens, Science **97**:2528 (June 11) 1943.

our stock solution of polyvinyl alcohol, generally, in accordance with the directions given by Downs. Fifteen grams of "PVA" (grade RH-349) powder is added slowly to 100 cc. of cold water in a beaker. The mixture is then stirred and heated in a water bath at a temperature of about 80 C. The heating process is continued until the solution attains the viscosity of thick molasses. Should undissolved clumps or particles remain, the solution is filtered through two layers of cheese cloth into a beaker. At this stage the solution may appear milky because of the inclusion of small air bubbles, but it later clears on further heating or standing. This stock solution may be stored for future use, after having been prepared in quantity.

By the addition of lactic acid and phenol to the stock solution of polyvinyl alcohol, Downs prepared a mounting medium which not only dehydrates but clears the specimen to be mounted in a satisfactory manner and hardens to provide a solid hyaline mount which requires no sealing in, as does a liquid mount. The use of this medium obviates the necessity for dehydration as in mounting in balsam or similar material. This is the mounting medium which we have used in our work. It is prepared by combining "PVA" stock solution 56 per cent, phenol 22 per cent and lactic acid 22 per cent by volume. In mixing, the lactic acid must be added first to the "PVA" stock solution before phenol is added, otherwise the "PVA" will change into a soft white sticky mass. In the mounting of cutaneous fungi we have added cotton blue dye to the lactophenol plastic in the proportion of 0.05 per cent. The dye provides a satisfactory degree of contrast in showing up fungus structures.

The "PVA" lactophenol medium is rapid and simple in use. The material to be mounted is placed on a clean dry grease-free glass slide, and a small quantity of the plastic is added, either the colorless medium or a medium to which the cotton blue dye has been added, and a cover slip is pressed into place. It is desirable to have some of the mounting medium flow out around the edges of the cover slip, as this aids in the sealing process. Within twenty-four to forty-eight hours excellent clearing of the specimen will have taken place and the specimen will be sealed in a semihard clear mount. A considerably longer period of time is required, however, before the plastic becomes completely hardened throughout and permanent in nature. Preparations may be handled and examined safely before complete hardening has taken place.

In the mounting of material removed from fungus cultures, a small amount of the agar containing the fungus is removed from the culture and placed on a slide, and the "PVA" lactophenol is caused to flow over and about it. If the cotton blue medium is used it is allowed to remain in contact with the fungus for thirty to sixty seconds before the cover slip is added, in order to allow the fungus structures to absorb

the stain. The dehydrating and clearing action of the medium takes care of the agar and its water content satisfactorily, and a permanent mount is provided for the fungus as it grows in situ. In slide cultures it is often possible to mount the fungus intact as it grows in culture by cutting out a thin section perpendicular to the surface. A convenient "knife" for the removal of such material from fungus cultures is provided by sealing a small piece of triangular-shaped platinum foil into the end of a solid glass stirring rod, which has been previously softened in a Bunsen flame.[4] A useful functional tool for the transfer of fungus material can be made from an inoculation needle inserted into a bacteriologic loop handle. The tip of the needle is heated in flame and bent about 4 mm. to a right angle.

Semitransparent mounts of scrapings of skin to demonstrate fungi may be prepared by transferring such scrapings directly from 70 per cent alcohol to the lactophenol plastic. While clearing is not as rapid nor as complete as with sodium hydroxide, a preparation is obtained in which the fungus structures may be readily seen. Only thin scales may be used with this method.

This mounting material, however, has its greatest field of usefulness in the making of permanent preparations from material removed from slide cultures and from ordinary fungus cultures growing on agar slants or on Petri culture dishes. In mounts of small arthropods, such as Sarcoptes scabiei or Phthirus pubis and its ova, the "PVA" lactophenol clears the object producing a transparency by which the details of its anatomic structure are clearly revealed. For the small arthropods with much body thickness, hollow ground or depression slides and circular cover slips are best adapted to the making of permanent preparations with the plastic. In the preparation of all types of mounts with the material, care should be taken to add a sufficient amount of the medium initially to allow for loss of substance due to evaporation of water through drying during the first few days.

SUMMARY

A plastic medium, polyvinyl alcohol with lactophenol, is described, which dehydrates and clears specimens and forms easily prepared, permanent, hard, hyaline mounts for the preservation of fungi and small arthropods of interest to dermatologists.

4. Dr. Ethel M. Rockwood made this suggestion.

ACRODERMATITIS PUSTULOSA PERSTANS (SO-CALLED PUSTULAR PSORIASIS)

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IN A RECENT article[1] histologic evidence was offered to show that the majority of cases of so-called pustular psoriasis were not related to psoriasis. We are reporting 11 additional cases to corroborate this view. In each of the 11 patients the eruption was limited to the palms, soles or both, and in no case was there a personal history or any clinical observations of psoriasis. In each case the microscopic picture was the same. In all the cases the Wassermann and Kahn reactions of the blood were negative, the urine was normal, no significant abnormalities were revealed in mycologic examinations and no foci of infection were detected.

REPORT OF CASES

CASE 1.—W. T., a white man aged 34, reported at the skin and cancer clinic in 1943 with a pustular eruption on the palms and soles, which had been present for eleven years with periods of remission. Roentgen rays and various ointments had been used, but with no benefit. The patient was treated while in the Navy (1941 to 1943). Clinically there were numerous discrete pustules on the palms and soles. There was no improvement after treatment with 5 per cent ointment of coal tar or with 2 per cent resorcinol and 5 per cent solution of coal tar in 70 per cent alcohol.

CASE 2.—H. A., a white man aged 53, was seen in 1939 with a pustular crusted eruption of one year's duration on the soles and left palm. During treatment with various ointments there were periods of remission. On examination in November 1945, pustular lesions were still present on the palms and soles. There was slight improvement from treatment with 5 per cent ointment of coal tar.

CASE 3.—S. F., a white man aged 45, was seen in 1939 with numerous isolated pustular lesions of six months' duration on the palms and soles. There were a few scaly lesions. There was no response to therapy with 10 per cent naphthalan,

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From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Sachs, W., and Scannone, F.: So-Called "Pustular Psoriasis," J. Invest. Dermat. **6**:349 (Dec.) 1945.

Photomicrograph showing a pustule within the epidermis and inflammatory reaction in the upper part of the cutis below the pustule.

5 per cent ammoniated mercury, 3 per cent salicylic acid, 5 per cent ointment of coal tar and resorcinol ointment.

CASE 4.—S. D., a white woman aged 45, was seen in 1939 with a pustular eruption of fifteen years' duration on the palms and soles. She had had a few periods of remission, but the present attack had persisted for over one year. The patient's mother had psoriasis. Treatment with 30 per cent sulfur ointment produced no improvement. However, there was some improvement from treatment with 5 per cent ointment of coal tar.

CASE 5.—F. M., a 46 year old white man, reported at the clinic in 1939 with a pustular eruption of a few months' duration on the palms and soles. Treatment

with coal tar, 30 per cent sulfur ointment and 0.5 per cent chrysarobin ointment resulted in no improvement.

CASE 6.—S. K., a white woman aged 40, had had a pustular eruption on the palms and soles, especially the heels, for the past seven years. On the palms were small isolated pustules, while on the soles there were large crusted pustular tender lesions. The lesions did not respond to 5 per cent ointment of coal tar. She had had one spontaneous remission two years previously, which lasted for one year.

CASE 7.—R. F., a 44 year old white man, was seen at the clinic in 1938. For one year there had been a pustular eruption on his palms and soles. The eruption did not respond to therapy, except that slight improvement occurred from treatment with 30 per cent sulfur ointment and 5 per cent ointment of coal tar.

CASE 8.—S. L., a 26 year old white man, entered the clinic with a pustular eruption on the palms and soles, which had persisted for one year. His history showed that the disease had developed while he was in the Army but that it had become more widespread soon after his discharge from the service. On examination, an erythematous pustular eruption was seen covering the palms, especially on the thenar eminences, and on the soles. Five per cent ointment of coal tar was ineffective. After an attack of influenza with fever the eruption improved somewhat.

CASE 9.—R. R., a white man aged 64, entered the clinic in 1942, complaining of an eruption on the posterior surfaces and tips of both large toes and on the left sole. He had had the dermatosis for the past twenty years, with periods of exacerbations and remissions. Examination disclosed small pustules on the tips and posterior aspects of the distal phalanges of both big toes. There were some scales, which seemed to be remnants of previous pustules. The nails of the affected toes were thickened, and there were similar lesions on the mesial aspect of the left sole. The patient had been treated with 5 per cent chrysarobin ointment, ointment of benzoic and salicylic acid and weekly doses of unfiltered roentgen rays (75 r) totaling 1,200 r, with no improvement. There had been definite improvement while he used a 5 per cent ointment of coal tar.

CASE 10.—M. B., a 44 year old white woman, was seen in the clinic in 1940 with an extensive pustular eruption, with crusting on the palms and soles. The duration had been five months. She presented a slight roughening of the elbows and knees, but no definite evidence of psoriasis. She was seen only once.

CASE 11.—M. K., a 47 year old man, was seen in the clinic in 1939 with a vesiculopustular eruption on the soles, especially the heels. He had had the eruption for four years, with the usual remissions. The patient improved slightly and temporarily while using ointment of lead oleate.

COMMENT

The eruption in each of the 11 patients was identified clinically as so-called pustular psoriasis by various members of the staff of the New York Skin and Cancer Unit and by one of us (G. M. M.). It was agreed that there was no clinical evidence or personal history of psoriasis in any case. In 1 instance the patient's mother had psoriasis. There was no psoriasis in the family history of 10 patients.

As is well known and as discussed by Sachs and Scannone [1] and others, there has been considerable controversy relative to the nosologic position of this disease. On histologic grounds one of us (W. S.)

has always contended that the disease is not psoriasis, while another (G. M. M.), largely on clinical grounds, had until recently believed that all cases represented an aberrant form of psoriasis.

The principal clinical characteristics of the disease are briefly as follows: The disease usually persists for a few years or many years, and there are spontaneous remissions and exacerbations. During remission there may be few or no elementary lesions, but the skin usually remains excessively dry, parchment-like and perhaps slightly scaly. The elementary lesion is a pustule, although at the beginning of an exacerbation it may be a vesicle, which soon becomes a pustule. The pustules are sterile, and they are distributed over any or all parts of the palms, soles, fingers and toes. Their predilection is for the thenar portion of the palms and the center of the soles, extending to the inner side of the feet.

As a rule the eruption is recalcitrant to all therapy. The disease in some patients responds favorably to the Goeckerman treatment. Some patients recover after the removal of a focus of infection, as a result of treatment with autogenous bacterial vaccine, or after a combination of both types of therapy. We believe that in many instances there is a spontaneous permanent cure, although the skin of the affected areas may remain parchment-like for many years after exacerbations of elementary lesions have ceased.

Some patients with the disease have psoriasis on other parts of the body, and the histologic architecture of the palmar and solar lesions is either definitely that of psoriasis or is compatible with it. Such cases may be designated as of psoriasis pustulosa or psoriasis with pustules. At times pustular psoriasis may be limited to the palms and soles. In such cases the diagnosis can be established only by a biopsy. Because some are cases of psoriasis, one of us (G. M. M.) had thought that all cases represented psoriasis, regardless of the histologic picture. As shown by Andrews and Machacek,[2] there are cases in which the eruption disappears after the removal of a focus of infection (pustular bacteride) and in which the histopathologic structure is not that of psoriasis.

It now appears that there may be three groups which may be clinically identical. The pustular bacteride may represent a small group. Pustular psoriasis certainly represents another small group. We now believe that the numerically largest group represents neither psoriasis nor a bacteride, but that it is an entity. The 11 cases herein reported belong to the last group. We offer the term acrodermatitis pustulosa perstans for the entity. The name is selected because the eruption is limited to the palms and soles, the pustules are of prime importance and the

2. Andrews, C., and Machacek, G. F.: Pustular Bacterids of the Hands and Feet, Arch. Dermat. & Syph. **32**:837 (Dec.) 1935.

eruption is persistent. Audry,[3] in 1900, called the disease acrodermatitis perstans because he thought that it was a form of *les acrodermatitis continués of* Hallopeau.[4] This concept has long been discarded.

Should it be accepted, the term pustular psoriasis may be reserved for psoriasis with pustules, regardless of location.

SUMMARY

Eleven cases of so-called pustular psoriasis are reported. All have exactly the same clinical and microscopic features. There was no evidence of psoriasis either clinically or microscopically, and with 1 exception there was no family history of psoriasis. The name acrodermatitis pustulosa perstans is suggested for what we believe may be regarded as an entity. The cause is unknown.

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3. Audry, C.: Les phlycténoses récidivantes des extrémités (acrodermatitis continues de Hallopeau), Ann. de dermat. et syph. **2**:913, 1901.

4. Hallopeau, H.: Sur une asphyxie locale des extrémités avec polydactylite suppurative chronique et poussées éphémères de dermatite, pustuleuse disséminée et symétrique, Bull. Soc. franç. de dermat. et syph. **1**:39, 1890.

NINTH DAY ERYTHEMA SHOWING PHOTOSENSITIVITY

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REPORTS on early erythema occurring after injection of arsphenamine began to appear in the European literature [1] shortly after the introduction of this type of treatment. But Milian [2] was the first to describe it under the name of "erythema of the ninth day" as an entirely separate entity which differs significantly from true arsphenamine dermatitis. He explained this syndrome on the basis of biotropism, i.e., the ability of certain drugs to stimulate latent micro-organisms to activity. According to Milian ninth day erythema is weakened measles, rubeola or scarlet fever, the micro-organisms of which were mobilized or the immunity to which was temporarily disturbed by arsphenamine. In fact, these types of erythema, with their generally morbilliform or scarlatiniform eruptions usually accompanied with constitutional symptoms, frequently simulate these acute infectious diseases. Yet Milian's theory was not accepted by most writers. Schreiner,[3] obtaining positive reactions in Prausnitz-Küstner passive transfer tests (thus far not confirmed by other investigators) suggested an allergic origin. Gjessing [4] and Cañizares and Thomas [5] incriminated the irritation of the autonomic nervous system in the causation of the syndrome. Keim [6]

From the Department of Dermatology, Hadassah Municipal Hospital.

1. (*a*) Brauer, A.: Zur Kenntnis der Salvarsandermatosen, Dermat. Ztschr. **19**:800, 1912. (*b*) Stühmer, A.: Ueber Neosalvarsan, München. med. Wchnschr. **59**:2447, 1912. (*c*) Wechselmann: Ueber Ueberempfindlichkeit bei intravenöser Salvarsaninjektion, Arch. f. Dermat. u. Syph. **111**:155, 1912. (*d*) Nicolas, J., and Moutot, H.: Trois ans d'arsénothérapie antisyphilitique, Ann. de dermat. et syph. **5**:391, 1914. (*e*) Guttmann, C.: Zur Frage der Weiterbehandlung mit Salvarsan nach Auftreten eines Salvarsanexanthems, Dermat. Ztschr. **23**:338, 1916.

2. Milian, G.: Les érythèmes arsenicaux du neuvième jour, Rev. de méd. **37**: 222, 1920.

3. Schreiner, K.: Ueber Milians "Erythem des 9. Tages," Arch. f. Dermat. u. Syph. **167**:94, 1932.

4. Gjessing, H. C.: A Form of Salvarsan Dermatitis (Ninth Day Erythema) in Which Salvarsan Treatment Is Continued, Acta dermat.-venereol. **9**:185, 1928.

5. Cañizares, O., and Thomas, E. W.: Early Acute Arsenical Erythemas: A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian, Arch. Dermat. & Syph. **39**:867 (May) 1939.

6. Keim, H. L.: "Erythema of the Ninth Day" Following Administration of Arsphenamine: Preliminary Report, Arch. Dermat. & Syph. **31**:291 (March) 1935.

incriminated not the arsenical but the phenol content liberated from the drug. Wainstein and Smelov,[7] reviewing 30 cases from Moscow, which were approximately 1 per cent of all their cases in which treatment was with neoarsphenamine, expressed the opinion that the cause of the syndrome is not uniform. Likewise, most authors do not agree with Milian that arsphenamine can be given with the same or even larger doses during the development of erythema. On the contrary, the recent general view of syphilologists is that caution should be exercised and that specific treatment be stopped. This caution is especially justified because, as Sweitzer[8] and Trow[9] rightly emphasized, the differentiation between ninth day erythema and true arsphenamine dermatitis is not always possible with certainty. Peters,[10] reporting 54 cases, concluded that arsphenamine should be withheld for at least one month after the recovery from the syndrome and treatment with it should then be resumed with smaller doses.

Of a number of cases of ninth day erythema which I have encountered, 2 that were recently seen were distinguished by their peculiar clinical course and particularly by the erythema's being confined only to the uncovered areas.

REPORT OF CASES

CASE 1.—Mr. V. Y., aged 41, who had emigrated to Palestine from Poland in 1924, was referred to the dermatologic clinic of the Hadassah Municipal Hospital for antisyphilitic treatment. His past history revealed that twenty-one years previously, while he was a soldier, he had received a course of treatment for approximately two months, consisting of intramuscular and intravenous injections for a penile sore. Three years later he married. His wife and three children remained healthy. In 1940 he voluntarily joined the British Army and served three years in Egypt and Libya. He was recently discharged from the army because of chronic rheumatic pains and a positive Wassermann reaction.

On Nov. 8, 1943, antisyphilitic treatment was instituted. On November 22, after receiving five injections of bismuth subsalicylate and two of neoarsphenamine and exactly nine days after the first injection of 0.45 Gm. of neoarsphenamine, a rash appeared on the neck and the upper extremities which became more pronounced in a few days and assumed a typical erythema multiforme character. Symmetrically, on the dorsa of both hands, the external aspects of the forearms, the lower thirds of the arms and the V-shaped area of the neck there were coin-sized and coin-shaped elevated papules or plaques of a reddish lilac color. He complained of a mildly burning sensation, but no fever or systemic symptoms were

7. Wainstein, A., and Smelov, N.: Sur le question de la symptomatologie, de la pathogénie et de la thérapeutique des exanthèmes précoces arsénobenzoliques —"érythèmes du neuvième jour" de Milian, Ann. de dermat. et syph. **8**:215, 1937.

8. Sweitzer, S. E., in discussion on Keim.[6]

9. Trow, E. Y., in discussion on Keim.[6]

10. Peters, E. E.: Syndrome of Milian's Erythema of the Ninth Day, Am. J. Syph., Gonor. & Ven. Dis. **25**:527, 1941; abstracted, Wise, F., and Sulzberger, M. B.: The 1940 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1941, p. 611.

present. The diagnosis of ninth day erythema was made, and the medication was stopped. The patient was presented at the meeting of the dermatologic society. The eruption gradually faded, after lasting eighteen days. The specific treatment was resumed on Jan. 6, 1944 and was well tolerated.

CASE 2.—G. B., a woman aged 42, who had emigrated twenty-five years previously from Russia, came to the dermatologic clinic on May 21, 1945. She presented a sharply defined brownish red patch, 8 cm. in diameter, with circular and serpiginous outlines on the upper outer surface of the left forearms, of three years' duration, and a similar but smaller lesion on the forehead, of one-half year's duration. The clinical picture was strongly suggestive of tuberoserpiginous syphilis. Her past history revealed that she had married at the age of 16, had two miscarriages and underwent a hysterectomy. The serologic reactions (Meinecke, Kahn, Rappaport) were strongly positive. Combined bismuth compound and neoarsphenamine therapy was started.

On July 15, ten days after the first injection of 0.3 Gm. neoarsphenamine, an erythematous maculopapular eruption developed, which spread rapidly and became confluent in places. Only the uncovered areas were involved: both cheeks, the sides and anterior parts of the neck, the backs of the hands, the forearms, the lower thirds of the arms and to a lesser degree the legs. She felt perfectly well except for a mild itching. She was seen almost every day. The eruption cleared completely after a week. Three weeks later 0.15 Gm. neoarsphenamine was given; this caused nausea, but further treatment was continued with no untoward reactions.

COMMENT

Although the main eruption of the syndrome is morbilliform or scarlatiniform, erythema multiforme has also been observed. Of the 11 cases of Cañizares and Thomas, 2 were of the erythema multiforme type, but the lesions were located also on the back. The relatively long duration of eighteen days in the first case is noteworthy. According to Peters the maximum limit of duration is twelve days. Neither of these patients had fever or other constitutional symptoms.

As to the special localization in the 2 cases, photosensitivity to arsenicals [11] and also to arsphenamine [12] has occasionally been observed, but, as far as I know, not of the type of ninth day erythema. On the other hand, these patients were not exposed to the sunlight during the treatment. In case 1 the disease occurred in November, but the patient's skin had been exposed to the sun and was considerably tanned after

11. (*a*) Ayres, S., Jr., and Anderson, N. P.: Cutaneous Manifestations of Arsenic Poisoning, Arch. Dermat. & Syph. **30**:33 (July) 1934. (*b*) Ayres, S., Jr.: Arsenical Dermatitis and Alopecia Areata Showing Photosensitivity, ibid. **31**:263 (Feb.) 1935.

12. (*a*) Jadassohn, J.: Bemerkungen zur Sensibilisierung und Desensibilisierung bei den Ekzemen im Anschluss an einen Fall von Odolekzem, Klin. Wchnschr. **2**:1680, 1923. (*b*) Juon, M.: Strahlenüberempfindlichkeit nach generalisierter Dermatitis infolge einer Salvarsan- und Hg-Kur, Arch. f. Dermat. u. Syph. **156**:355, 1928. (*c*) Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Photodynamic Effects in Dermatology, Am. J. M. Sc. **203**:608, 1942.

lengthy service in the Western Desert. The second patient had fair skin, and her exposed areas were rather tanned after a twenty-five year stay in this country. In the classic cases of photosensitivity too—in pellagra, for example—it is believed that the characteristic cutaneous changes are frequently not due to direct irradiation by the sun. The skin which has been altered by the sun and light possesses a lower resistance and is more susceptible to sensitization. The damaged skin plays some role in the localization of the common arsphenamine dermatitis (Silberstein,[13] Keim), but no such relation is so far known in the disease under consideration. Nevertheless, the impression is that in the cases herein reported damage to the skin by the sun might be in a great degree responsible for the special localization of erythema.

SUMMARY

Two cases of nineth day erythema are described. The eruption, which was the only clinical manifestation of the syndrome, was strictly limited to the exposed areas. I believe that previous damage to the skin by sunlight was responsible for this special localization.

9 Montefiore Street.

13. Silberstein, S.: Zur Pathogenese der Salvarsandermatitis und über den Arsennachweis in der Haut nach Salversanbehandlung, Arch. f. Dermat. u. Syph. **144**:260, 1923.

STUDIES ON SENSITIVITY TO SULFONAMIDE OINTMENTS

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AND
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ST. LOUIS

MANY reports in the literature emphasize the frequent occurrence of cutaneous sensitivity following the topical application of the sulfonamide group of drugs. Darke [1] treated 218 patients with injuries of a minor surgical nature with a 5 per cent sulfathiazole cream and observed 12 instances in which sensitivity developed (5.5 per cent). Inges [2] treated 300 patients with sulfathiazole and sulfadiazine in salves, powders and lotions. Sensitivity reactions were observed in 10 patients (3.3 per cent). Robert [3] observed 4 cases of hypersensitivity to sulfathiazole ointment when making patch tests on 200 patients who had never been treated with sulfathiazole. Cole,[4] in the report for the Council on Pharmacy and Chemistry of the American Medical Association, reviewed the literature on the local use of the sulfonamide compounds in dermatology. He advised that sulfonamide drugs should not be applied locally for more than five days because of the danger of sensitization.

This study was performed to determine what percentage of a group of 200 volunteers could be sensitized to three different sulfonamide ointments. An attempt was made to test the same persons with all three ointments in an effort to determine whether sensitivity to one sulfonamide drug predisposed to sensitivity to another.

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Studies, observations and reports are from the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, Service of Dr. M. F. Engman Sr.

1. Darke, R. A.: Sensitivity to Topical Application of Sulfathiazole Ointment, J. A. M. A. **124**:403-404 (Feb. 12) 1944.

2. Inges, A. E.: Dermatoses: Local Treatment with Sulfathiazole and Sulfadiazine, California & West. Med. **58**:269-272 (May) 1943.

3. Robert, P.: Uses of Sulfonamides in Dermatology, Schweiz. med. Wchnschr. **73**:627-632 (May 8) 1943.

4. Cole, H. N.: Chemotherapy in Dermatology, J. A. M. A. **123**:411-417 (Oct. 16) 1943.

OINTMENTS

The three sulfonamide ointments submitted for patch tests were: (1) a 5 per cent sulfadiazine ointment, with the ointment base adjusted to p_H 7 to 7.5, (2) a 5 per cent sulfathiazole ointment, p_H 7 to 7.5 and (3) a 5 per cent sulfadiazine ointment, p_H 8.1, so that the sodium salt of sulfadiazine was present.[5] The ointment base was water miscible and contained "daxad, no. 11," a polymerized alkyl aryl sulfonate (Dewey Almy Co.); "santomerse, 3," an alkylated aryl sulfonate (Monsanto Chemical Co.); glycerine; phenyl mercuric acetate, a fungicide; glyceryl monostearate; stearic acid, triple pressed; anhydrous wool fat U. S. P.; liquid petrolatum U. S. P., sodium chloride and water.

PROCEDURE IN PATCH TESTS

The patch tests with the sulfonamide ointments were performed according to the procedure recommended by Schwartz and Peck.[6] The type of test used has been designated as the "prophetic patch test" technic and is used to determine whether or not a substance will produce dermatitis after contact with the skin. Two separate tests are made ten to fourteen days apart, on the same person. Two hundred persons are used, just as in other standard studies with patch tests. It is presumed that reactions will occur in the first series if the material tested is a primary irritant, provided that the person under observation has never had previous contact with the substance. The reactions caused by the second series of tests indicate the number of persons in whom sensitivity has been induced by the first patch test.

A group of about 200 volunteers was tested with each ointment—223 for (1), 210 for (2) and 200 for (3). These volunteers were factory employees and patients at two of the St. Louis hospitals. The ages of the volunteers ranged from 16 to 70 years. The two sexes were fairly equally represented. An attempt was made to test the same persons with all three of the ointments, but this was not possible with the first sulfadiazine ointment.

The technic employed was as follows: 1. The sulfadiazine (or sulfathiazole) ointment and the ointment base, which was used as a control, were applied to pieces of gauze ¼ inch (0.6 cm.) square and covered with standard "elastopatch" (Duke Manufacturing Company). 2. The patches were placed on the scapular and infrascapular areas, on the back of the arms and on the anterior and internal surfaces of the thighs. 3. The patches were removed approximately forty-eight hours later

5. Information supplied to us indicated that at a p_H of 7 to 7.5 only minute amounts of the sodium salts of sulfathiazole or sulfadiazine would be available.

6. Schwartz, L., and Peck, S. M.: The Patch Test in Contact Dermatitis, Pub. Health Rep. **59**:546-557 (April 28) 1944.

and the areas observed. The areas were again observed in ninety-six and one hundred and twenty hours. 4. When ten or more days had elapsed after the removal of the first patches, the patches were reapplied and steps 2 and 3 repeated.

RESULTS

With the 5 per cent sulfadiazine ointment (base p_H 7 to 7.5), 4 of the volunteers demonstrated positive reactions in the first test. Two of these volunteers gave no history of ingestion of or exposure to any of the sulfonamide drugs. The third person had experienced dermatitis after the oral administration of sulfathiazole, and the fourth had been exposed to sulfadiazine ointment in her work.

In the second test, 6 volunteers demonstrated reactions[7] of 1 plus to patch tests with the ointment. One of them reacted to the ointment

Results of Tests with Sulfonamide Ointments

	Case and Subject	Sex	Sulfadiazine (p_H 7-7.5) First Test	Sulfadiazine (p_H 7-7.5) Second Test	Sulfathiazole (p_H 7-7.5) First Test	Sulfathiazole (p_H 7-7.5) Second Test	Sulfadiazine (p_H 8.1) First Test	Sulfadiazine (p_H 8.1) Second Test
1	V. J.	F	+	—	..	..	..	..
2	E. S.	F	+	—	..	..	..	..
3	M. A.	F	+*	..	..	..	..	..
4	O. A.	M	+†	..	..	..	..	..
5	E. S.	F	—	+	..	..	..	..
6	E. L.	F	—	+	..	..	..	..
7	B. O.	F	—	+	..	..	..	..
8	J. A.	M	—	+	..	..	..	..
9	F. K.	F	—	+	..	..	..	..
10	S. A.	F	—‡	+‡	..	..	..	..
11	A. K.	F	..	..	++	—	—	—
12	P. B.	M	..	..	++	—	++	—
13	L. B.	F	—	—	—	+	—	—

* This subject had contact with sulfadiazine.
† This subject had a cutaneous eruption after taking sulfathiazole orally.
‡ S. A. reacted to the base.

base to the same extent as to the ointment base plus the sulfadiazine, and results for this subject are not included in the final tabulation.

With the 5 per cent sulfathiazole ointment (base p_H 7 to 7.5), 2 volunteers demonstrated positive reactions in the first test. None of these reacted to the ointment base. There was no history of exposure to sulfathiazole in these 2 volunteers, and on further testing (with the sulfadiazine ointment base p_H 8.1) 1 of these demonstrated positive and 1 negative reactions.

In the second test only 1 volunteer had a positive reaction to the sulfathiazole ointment and not to the base. This volunteer had been tested with both sulfadiazine ointments with no reaction.

7. One plus was a reaction of erythema, 2 plus erythema and edema, 3 plus erythema, papules and a few vesicles and 4 plus erythema, edema, many vesicles and, in some cases, ulceration.

With the 5 per cent sulfadiazine ointment (base p_H 8.1), only 1 volunteer demonstrated positive reactions to this sulfadiazine ointment in the first patch test. He reacted to the 5 per cent sulfathiazole ointment in the same manner. He denied any exposure to sulfonamide drugs.

None of these volunteers reacted in another patch test with this sulfadiazine ointment.

COMMENT

The number of persons sensitized to the sulfonamide ointments by means of patch tests was small. Only 2.3 per cent were sensitized to the first sulfadiazine ointment; none were sensitized to the second sulfadiazine ointment, and 0.49 per cent were sensitized to the sulfathiazole ointment. A higher percentage of sensitizations to the sulfonamide drugs was observed by others [8] who were using sulfonamide ointments in the treatment of superficial infections and injuries. However, in the patch test the material is applied only once, in only a small amount and to one area of the skin. Under actual conditions of use of such an ointment the opportunity for sensitization may be much greater, as the ointment may be applied several times during the day and over large surfaces. The actual area exposed in such applications might be a factor in cutaneous sensitization. Further work should be done to determine whether the amount of the drug, the frequency of application and the area of surface to which it is applied play any part in the frequency of sensitization to the sulfonamide drugs.

It was hoped that something would be learned about the frequency of cross reactions from different sulfonamide drugs. However, there were not enough sensitive volunteers available for further testing to permit us to determine the frequency of such reactions.

SUMMARY

A group of 223 volunteers was given patch tests with a 5 per cent sulfadiazine ointment (base p_H 7 to 7.5). Two hundred and ten volunteers had patch tests with a 5 per cent sulfathiazole ointment (base p_H 7 to 7.5). Two hundred volunteers had patch tests with a 5 per cent sulfadiazine ointment (base p_H 8.1). Of these volunteers 2.3 per cent were sensitized to the first sulfadiazine ointment; 0.49 per cent were sensitized to the sulfathiazole ointment, and none were sensitized to the second sulfadiazine ointment.

CONCLUSIONS

In view of the many clinical reports on sensitivity to the sulfonamide drugs, we are not sure that the results reported here are valid. It is

8. Darke.[1] Inges.[2]

our feeling that epithelial sensitization may take place with greater facility when the sulfonamide drugs are used on previously inflamed skin and over larger areas of surface.

It is pertinent that probably hundreds of thousands of persons have been treated locally with the sulfonamide drugs, while, perhaps, only a few thousands have shown phenomena of cutaneous sensitization. We are, therefore, inclined to change the views which we had previously expressed, namely, that the sulfonamide drugs are highly potent cutaneous sensitizers. We would like to qualify that opinion by saying that the sulfonamide drugs are probably highly potent sensitizers when they are applied over relatively large areas of skin and particularly on damaged skin. Moreover, we believe that when the sulfonamide drugs are used on the skin for more than five days the probability of sensitization is greatly increased.

SUPPURATIVE RINGWORM CONTRACTED FROM CATTLE

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DURING the past three years, we have observed a series of 23 cases of deep suppurative ringworm infections which were contracted from cattle. In the large majority of the cases the organisms were difficult to isolate and produced slowly growing, glabrous colonies which were identified as belonging to the faviform group of trichophyta. In a few cases the rapidly growing, fluffy colonies of the gypseum trichophyta were obtained.

Since the lesions were of a deep suppurative character—a type of trichophyton infection which, according to Conant and his colleagues,[1] is rarely seen in this country—and since the incidence of the transmission of ringworm infection from livestock to farm workers is not generally known or recognized, we feel that these cases should be reported. Also the high incidence of the faviform trichophyta observed in these infections and the difficulty encountered in their isolation and identification emphasize the importance of a study of these organisms as causative agents of animal ringworm which may be transmitted to man.

According to Hagan,[2] ringworm is a common disease of cattle in this country and especially of their young, and human infection occasionally occurs. The chief cause of ringworm in cattle appears to be the common ectothrix trichophyton, Trichophyton mentagrophytes, or other members of the gypseum group. However, the faviform trichophyta, Trichophyton album, Trichophyton discoides, Trichophyton ochraceum and Trichophyton verrucosum are known to be causative

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1. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Military Medical Manual, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1944.

2. Hagan, W. A.: The Infectious Diseases of Domestic Animals, Ithaca, N. Y., Comstock Publishing Company, 1943.

agents of ringworm in cattle and horses.[3] Most of the veterinary literature indicates that ringworm infection of cattle and horses may occasionally be transmitted to man, but the incidence of this type of infection in the United States is not generally known. In 1938, Gammel and Work[4] reported that during a period of fourteen years they observed only 4 cases of ringworm which had been contracted from livestock. Cultural studies showed that the infection in 3 of these cases was caused by Trichophyton gypseum, and in 1 case (apparently contracted from "scabby" sheep) was caused by one of the faviform trichophyta, T. album (var. singulare).

Human infection with the faviform trichophyta was first observed in France by Sabouraud in 1893.[5] During his career Sabouraud reported only 9 cases. Sporadic reports have come chiefly from Western Europe, the Balkans and North Africa. The incidence of the infection in Yugoslavia appears to have been relatively high. Georgjević and Milochevitch[6] observed T. album to be a causative agent in 81 of 241 cases of dermatomycoses in that country. The disease has been reported from Uruguay[7] and Mexico.[8] In 1934 Davidson, Gregory and Birt[9] reported 28 cases from Canada, and in 1938 Gammel and Work[4] reported 1 case in the United States. In all of the cases the source of infection was believed to be livestock.

The most common type of lesion described in human infections with the faviform trichophyta is of a suppurative character and includes all the lesions which attack the deeper layers of the skin and the hair follicles, producing nodules with suppuration. Other types of lesions, however, have been reported. The first lesion described by Sabouraud[10] was a flat plaque on the glabrous skin, with an impetiginized surface and flat crusts. He also described lesions resembling plaques of sebor-

3. Hutyra, F., and Marek, J.: Special Pathology and Therapeutics of Diseases of Domestic Animals, ed. 4, London, Ballière, Tindall & Cox, 1929, vol. 3.

4. Gammel, J. A., and Work, J. L.: Sycosis Parasitica Due to Favotrichophyton Album Var. Singulare, Arch. Dermat. & Syph. **38**:756-772 (Nov.) 1938.

5. Sabouraud, R.: Contribution a l'étude de la trichophytie humaine, Ann. de dermat. et syph. **4**:814-835, 1893.

6. Georgjević, G., and Milochevitch, S.: Aspects cliniques de trichophytie et de favus provoqués par le Trichophyton faviforme album, Ann. de parasitol. **13**:243-252, 1935.

7. Mackinnon, J. E.: Epizootia de tiña en caballos y contaminación del hombre, Arch. urug. de med., cir. y especialid. **8**:498-502, 1936.

8. Ochoterena, I.: Une nouvelle espèce de champignon producteur de teignes sabouraudites (aleurocloster) ueniae octerena, Rev. mex. biol. **4**:94-100, 1924.

9. Davidson, A. M.; Gregory, P. H., and Birt, A. R.: Clinical and Mycological Study of Suppurative Ringworm, Canad. M. A. J. **31**:587-591, 1934.

10. Sabouraud, R.: Les trichophyton faviforme, Ann. de dermat. et syph. **9**:609-635, 1908.

rheic dermatitis and young lesions which were dry and leathery in appearance. One case, illustrated in "Les teignes,"[11] presented well defined, round plaques with erythematous vesicular borders and white scaly centers which become confluent, forming large polycyclic lesions. Georgjević and Milochevitch[6] described a clinical type of lesion due to T. album, which they stated was clinically identical with the lesion typical of classic favus infection.

The common ectothrix trichophyta of the gypseum group are known to produce both a superficial and a deep type of cutaneous infection. The superficial type, the most commonly seen, presents oval, round or annular scaling lesions, usually clear in the center and surrounded by a vesicular border. The deep type of infection is characterized by suppurative lesions of the sycosis, kerion or agminate folliculitis types.

REPORT AND SUMMARY OF CASES

The 23 cases of suppurative ringworm which we have observed (1942 to 1945) occurred in a community of farming families in central Pennsylvania. In all instances there was a history of recent contact with cattle, and in all but 5 cases the patients had observed ringworm lesions on the animals. Three cases were contracted secondarily from members of the family previously infected from the cattle.

Cultural studies indicated that 14 of the 23 cases had been caused by faviform trichophyta, 12 cases by T. discoides and 2 cases by T. album. Four cases yielded the common gypseum type of trichophyton, T. mentagrophytes. In the remaining 5 cases in this series, no parasitized hairs were observed and no cultures that were positive for fungi were obtained. However, the nature of the lesions, the absence of bacterial infection and the history of contact with ringworm-infected cattle indicated that the 5 cases also were of ringworm contracted from cattle.

The lesions presented were all of a deep suppurative type. They occurred, in order of frequency, on the neck, face, wrists, forearms and in the occipital region of the scalp. The cases in this series may be roughly divided into three groups: the parasitic sycosis type, or suppurative ringworm of the bearded areas of the face and neck, the kerion type, observed on the scalp and also on the bearded areas of the face and neck, and agminate folliculitis, or suppurative lesions of the glabrous skin. In the following report the general characteristics of each type of lesion are described and 2 rather atypical cases are presented in detail.

Parasitic Sycosis.—Seven of the patients observed presented deep suppurative lesions of the bearded areas of the face and neck. The

11. Sabouraud, R.: Les teignes, Paris, Masson & Cie, 1910, vol. 3.

infections started as follicular pustules, which later formed large firm nodular abscesses with thick gummy crusts, through the openings of which heavy pus could be expressed. The hairs were easily removed from the lesions, and few hairs remained in the older lesions. The majority of the patients felt no pain. Aside from the local discomfort which the lesions produced they felt well and were otherwise in good health. Two patients who had extensive involvement of the face and neck presented lesions also on the upper part of the chest and forearms. T. discoides was isolated in 4 of the cases. (A coexisting infection with Streptococcus hemolyticus was observed in 1 case.) T. album was isolated in 1 case and T. mentagrophytes in 1 case. In the remaining case cultures were negative for both bacteria and fungi.

One case in this group did not present the typical suppurative lesions when first seen. The patient stated that for three weeks he had noticed a "redness" which

Fig. 1.—Parasitic sycosis caused by T. discoides. *A*, early stage in which superficial ringworm preceded the development of deep suppurative lesions. *B*, later stage in which suppurative lesions are well developed.

had appeared at the site of an acid burn on the left side of the neck. The erythema spread over both sides of the neck and face after the burn itself had healed. In these areas there developed many raised, annular and polycyclic lesions, typical of superficial ringworm (fig. 1). No vesicles were observed at the borders, although the patient stated that he had had vesicles in these areas. He had a small coin-sized lesion in the left sternoclavicular area. (These lesions appeared to be similar to those described by Sabouraud in a case due to T. album.[11])

Examination of scales from the borders of the lesions and of hairs from these areas did not reveal any spores or mycelial elements. Three per cent ammoniated mercury was applied. After a week the whole process had improved and some of the areas had healed completely. However, several pustules had appeared on one side of the face. Five days later he had more pustules, and in front of the left ear there was an area 5 cm. in diameter with many red, deeply infiltrated pustules.

Examination of hairs, scales and pus from these affected areas still did not reveal any spores or mycelial elements, but because of the nature of the lesions and the fact that this patient was a farmer and cared for cattle, it was suspected that he was experiencing the deep suppurative type of ringworm infection which had been observed in other patients. The patient was given 2 Gm. of sodium iodide intravenously, 10 drops of sodium iodide was to be taken orally three times a day, and ointment with 20 per cent sulfathiazole sodium was prescribed for local application.

Four days later the patient returned with enormous swelling of the face. The oral temperature was 102 F, the white blood cell count was 21,000, and the patient was obviously ill. He had difficulty in eating, because of the swelling and pain in his face, and had not been able to sleep. The bearded area of the face was now covered with heavy gummy crusts, from under which thick creamy pus was oozing at many points. When pieces of the crust were removed many large pustules were observed. At this point the eruption was typical of the deep suppurative ringworm which we had previously observed, except that the process was more extensive and the patient was decidedly ill (fig. 1 *B*). Smears of the pus now showed many large gram-positive spores, some of which occurred in short chains. A large number of hairs were examined in sodium hydroxide preparations, but only a few were observed to be parasitized. These showed large-spored, ectothrix parasitism. Cultures of hairs and pus were made, and typical colonies of T. discoides were obtained. There was no evidence of bacteria infection either in the smears or in cultures of the pus made on blood agar plates.

A few days after the onset of this extensive eruption, a faint pink, macular eruption developed on the flexor surfaces of the forearms and the inner surfaces of the thighs. This disappeared spontaneously in a week. The treatment with iodides was continued and the patient gradually began to improve. After three weeks of treatment the white blood cell count fell and the temperature returned to normal. There were still many pustules, but the pus could be expressed more easily, and there was much less swelling of the face and chin. Treatment with the sulfathiazole ointment was then discontinued, but the patient was still given 2 Gm. of sodium iodide orally. Three months after the first appearance of the pustules the improvement was great. There were only a few pustules, a few large plugs and a number of small comedos. There were reticular scars throughout the subcutaneous tissue, and in a few areas there were fibrous nodules. Cultures were negative.

Another patient in this group presented lesions which were complicated by bacterial infection. There was a history of swelling of the lower part of the right cheek of a month's duration. He had had frequent contact with infected cattle, which he described as being "covered with flat white scabby sores about the eyes and mouth." He stated that he had cured several small lesions on himself with tincture of iodine.

He presented a large red indurated lesion on the right side of the chin, with many openings through which pus exuded. The lesion measured 7 cm. in diameter, and the whole surface was covered with a honey-colored exudate. There were several small superficial lesions about the face with thick, "stuck-on," honey-colored crusts. His oral temperature was 100 F., and his white blood count 20,700. He appeared tired and ill, and the whole face was swollen. Smears of the pus showed many gram-positive cocci in chains and large gram-positive spores, which occurred singly or in short chains. Culture of the pus on blood agar revealed a hemolytic streptococcus and a fungus which was identified as T. discoides. The patient was

treated with sulfathiazole, 1 Gm. every four hours, and 5 per cent sulfathiazole ointment was used locally. Three weeks after the first visit the swelling and tenderness subsided and there were no pustules remaining. The oral temperature was normal, the white blood count had fallen to 9,000, and cultures were negative for both bacteria and fungi.

Kerion Lesions.—Seven of the patients observed presented kerion lesions on the bearded areas of the face, in the hairy parts of the posterior cervical region and in the occipital region of the scalp (fig. 2). The lesions of the scalp all occurred in children between the ages of 4 and 11. The kerions in the posterior cervical region and on the face occurred in men. The lesions appeared as large boggy masses which arose abruptly from the surrounding tissues. They were dark red

Fig. 2.—Kerion lesion produced by T. discoides; *A*, of the posterior cervical regions, and *B*, of the posterior cervical region and cheek.

and dotted with perifollicular abscesses. The hairs were lusterless and broken off, and in some instances they had been shed completely. In 6 cases T. discoides was isolated. In 1 case no parasitized hairs were observed and no fungi or bacteria were obtained from cultures. The lesions of the scalp were healed much more slowly than the lesions of the less hairy areas of the skin.

Agminate Folliculitis of the Glabrous Skin.—Fourteen patients sustained suppurative lesions of the glabrous skin. These occurred chiefly on the wrists and forearms (fig. 3). Five in this group also had suppurative lesions of the bearded areas or of the scalp. All of the lesions of the glabrous skin were characterized by groups of dark red nodules dotted with perifollicular pustules. Many of the hairs were loose. Pus

could usually be expressed from the lesions by gentle pressure. In no case, however, did the lesions show the deep suppurative sinuses observed in the lesions of the scalp or the heavy gummy crusts observed on the face. In 1 of the patients, who had had a lesion on the extensor surface of the forearm for a period of six weeks, numerous small vesicles developed over the fingers of both hands. These, it was concluded, were probably trichophytids. They disappeared spontaneously in a week. Cultures from the lesions of the glabrous skin were not as successful as from the more inflammatory lesions of the beard or scalp. However, in 6 cases T. discoides was isolated. In 3 cases T. mentagrophytes was obtained.

Fig. 3.—Agminate folliculitis. Lesion of extensor surface of right forearm, caused by T. discoides.

TREATMENT AND CLINICAL COURSE OF THE INFECTIONS

Local treatment of the lesions with such remedies as 3 per cent ammoniated mercury, merthiolate ointment, 1 to 2,000, and 5 per cent sulfathiazole ointment proved to be of little value in most of the cases. On small superficial lesions tincture of iodine was effective if used when the lesion first occurred. In the cases in which the lesions were deep and suppurative, the course of treatment which appeared to be most effective was the use of iodides intravenously and by mouth. Usually the patient was given an intravenous injection of 2 Gm. of sodium iodide at the first visit and instructed to take 5 to 15 drops of a saturated solution of sodium iodide three times a day. Injections were repeated at successive visits, and oral therapy continued until the lesions had healed. In several cases, 5 per cent sulfathiazole ointment or

merthiolate ointment 1 to 2,000 was used locally with the iodide therapy, to control any associated bacterial infection. In cases in which the lesions were small and more superficial the injections of iodides as well as the local therapy were omitted, and only the iodides orally were prescribed. The lesions usually showed definite improvement with iodide therapy at the end of the first week. The smaller lesions healed in three to four weeks, but the deeper more extensive lesions took four to six weeks for complete cure. Manual epilation of hairs and draining of the pustules aided the healing process.

The benefit of topical therapy with sulfonamide compound was questionable. In 1 case, however, in which a coexisting bacterial infection due to S. hemolyticus was present, the use of sulfathiazole orally and locally cleared the bacterial infection and dealt as satisfactorily with the fungous infection as did the iodides.

EVIDENCE FOR THE ANIMAL ORIGIN OF THE INFECTIONS

That human infection with the faviform trichophyta are always either directly or indirectly of animal origin has become evident from the literature. The majority of cases reported have occurred among farm workers, especially workers concerned with the care of cattle.[12] There is also evidence that faviform trichophyton infections have been contracted from horses,[13] from a donkey,[10] from sheep [4] and from a goat.[14]

In this series of 23 cases of suppurative ringworm, 16 of the patients were men, all of whom were farmers who cared for cattle. One woman lived on a farm and did milking. The 5 children in this series all lived on farms. Three of these children had apparently contracted the infection secondarily from older members of the family who had active lesions. In all but 1 instance, in which the patient had not been questioned, patients with primary infections due to the faviform trichophyta gave a definite history of contact with cattle bearing typical ringworm lesions. This was confirmed in several instances by the local veterinarians who were treating the cattle for ringworm. In 1 case hairs obtained from the infected cattle presented the typical large-spored ectothrix parasitism seen in infections due to the faviform trichophyta. T. discoides was isolated from hairs obtained from other cattle.

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12. Ashton, G.: Cattle Ringworm in Man, Lancet **1**:97-99, 1932. Milochevitch, S.: Trichophyton immergens et ses manifestations cliniques, Mycopathologia **1**:88-97, 1938. Kister, J., and Delbanco, E.: Zur Kasuistik der Kälberflechte, Arch. f. Dermat. u. Syph. **130**:484-486, 1921.

13. Hagan.[3] Mackinnon.[7] Sabouraud.[10]

14. Catanei, A., and Izac, R.: Nouvelle teigne d'origine animale observée chez un indigène algerien, Arch. Inst. Pasteur d'Algérie **19**:339-341, 1941.

It is important to note that T. mentagrophytes was isolated in 4 instances from patients with deep suppurative lesions. The patients also were farmers and had contact with cattle, but in none of the cases had the patients observed ringworm on their cattle. The source of the infection with T. mentagrophytes is therefore unknown, but because the patients presented suppurative lesions grossly identical with the lesions caused by the faviform trichophyta it seemed important to include them in this series. It seems highly probable that these infections were also cattle borne, as reports in the veterinary literature indicate that T. mentagrophytes is a common cause of ringworm in cattle and may be transmitted to man.[2]

The gross lesions in cattle caused by the faviform trichophyta are similar to lesions produced by any of this genus of fungi. They occur chiefly on the head and neck and in the anal region. They are typically flat, raised, grayish white, well defined plaques, from which broken hairs protrude. If the crusts are pulled off, a moist bleeding surface will be exposed. Pus may accumulate beneath the crusts. After one to two months the crusts come off and leave a bald patch, in which desquamation occurs for a time. This subsequently heals, and the area becomes covered with hair. In calves the lesions usually occur about the mouth and have a thick branlike appearance. The faviform trichophyta will produce pure endothrix as well as ectothrix parasitism of the hair of cattle. It has been observed that in calves frequently only the endothrix parasitism occurs.[15]

EXAMINATION AND CULTURAL STUDIES OF CLINICAL MATERIAL

Examination of hairs, scales and pus was made in all cases presented in this series. In infections due to T. mentagrophytes parasitized hairs were readily demonstrated. However, in infections due to the faviform organisms examination of a large number of hairs was usually required before evidence of parasitism could be observed. In both types of infection the spores are arranged in chains, forming a sheath on the outside of the hair, and mycelial threads can be seen in the interior of the hair itself (fig. 4). The spores of the faviform trichophyta are larger than those of the gypseum group of trichophyta, but the size of the spores is difficult to ascertain in routine examination of parasitized hairs. Culture of the hairs is necessary to determine the causative organism.

Examination of the scrapings from the skin did not reveal mycelial elements in all cases, and cultures from this material were negative for fungi.

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15. Carol, W. L. L.: A Case of Infection with Trichophyton Faviforme Album, and a Case of Infection with Microsporon Orientale (New Species), Urol. & Cutan. Rev. **32**:19-23, 1928. Baudet, E. A. R. F.: Particularités d'une teigne megasporée d'un veau, Ann. de parasitol. **8**:520-522, 1930.

In well developed lesions gram-stained smears of the pus showed large gram-positive spores, which occurred singly and in short chains. The presence of spores in the pus greatly facilitated the attainment of pure cultures.

In 4 cases, T. mentagrophytes was isolated on Sabouraud's maltose agar ("difco"). Typical white, powdery to fluffy colonies, with all the structures typical of the trichophyton group, appeared within ten days. In many cases, however, in which material from the deep suppurative lesions was used as an inoculum, the Sabouraud maltose agar remained sterile. In most instances it was observed that the blood agar plates (prepared with blood agar base ["difco"], 5 per cent citrated human blood), which were also used routinely in all cultures from suppurative lesions, supported the growth of a fungus which would not grow, even when transplanted, on the maltose agar. These fungi, which could be isolated on the blood agar base (the addition of the blood to this medium was of no advantage) and which could not be isolated or grown on the maltose agar, were later identified as the faviform trichophyta, T. album and T. discoides.

Investigations of the requirements for growth of T. discoides by Robbins, Mackinnon and Ma [16] have shown that this organism suffers from complete deficiencies for pyridoxine, inactive inositol and molecular thiamine and partial deficiencies for unidentified substances present in peptone, casein hydrolyzate, hydrolyzed egg albumin, malt extract, gelatin and filtrate (DR fraction) from white potatoes. The authors demonstrated that vigorous growth could be obtained on a thiamine and peptone medium.

Our successful isolation of the faviform trichophyta (T. album and T. discoides) on blood agar base indicated that this medium supplied the necessary factors for growth which were absent in Sabouraud's maltose agar. Blood agar base successfully supported the typical glabrous vegetative growth of the faviform trichophytons, producing colonies which resembled clearly the colonies described by Sabouraud on his classic proof mediums. (The original classic proof mediums of Sabouraud undoubtedly contained many growth substances which are absent in the more purified products used in the artificial mediums now commercially available.) On Sabouraud's proof medium, which we were able to reproduce, and on the blood agar base, T. album typically produces a glabrous spongy heaped-up vermicular colony of the color of wax. This may become dark tan to brown after several weeks, and some white powdery growth may appear at the base of the acuminate colony (fig. 5*A*). T. discoides produces on these mediums a colony

16. Robbins, W. J.; Mackinnon, J. E., and Ma, R.: Vitamin Deficiences of Trichophyton discoides, Bull. Torrey Club **69**:509-521, 1942.

which is also habitually glabrous, but has a fairly regular disk shape and a small raised center which may or may not be present. The colony frequently has a grayish tan to grayish yellow pigment and has a powdery or velvety surface of short fine white down (fig. 5*B*). Microscopic examination of these glabrous colonies reveals irregular mycelia with an abundance of irregularly formed intercalary and terminal chlamydospores. The appearance is similar to the "favic chandeliers" seen in

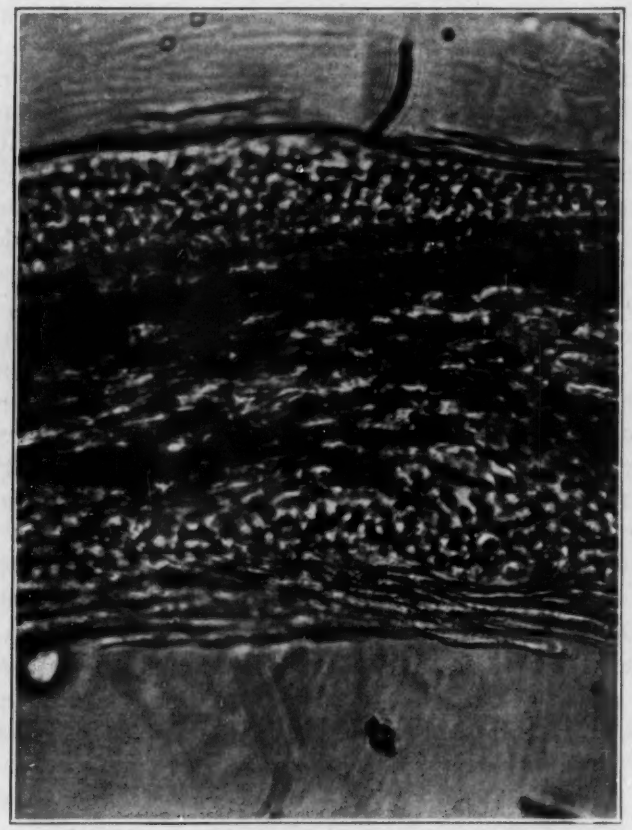

Fig. 4.—Typical hair, showing ectothrix parasitism by T. album.

the causative organism of favus. Spore-bearing structures are characteristically absent.

The addition of thiamine to the blood agar base, 0.1 mg. per hundred cubic centimeters, improves this medium for purposes of isolation. On the medium enriched with thiamine, growth may appear in some instances five days after inoculation, and vigorous colonies are produced with white fluffy surface growth (fig. 5 [*C* and *D*]). The colonies show all the structures (microconidia and macroconidia) which are characteristic

of the trichophyton group (fig. 6). After growth on the enriched medium, transplants may be made to a medium with less thiamine content, such as plain blood agar base ("difco") or Sabouraud's maltose agar ("difco"), on which the typical glabrous characteristics of the colonies, used in identification of the various species, are more apparent.

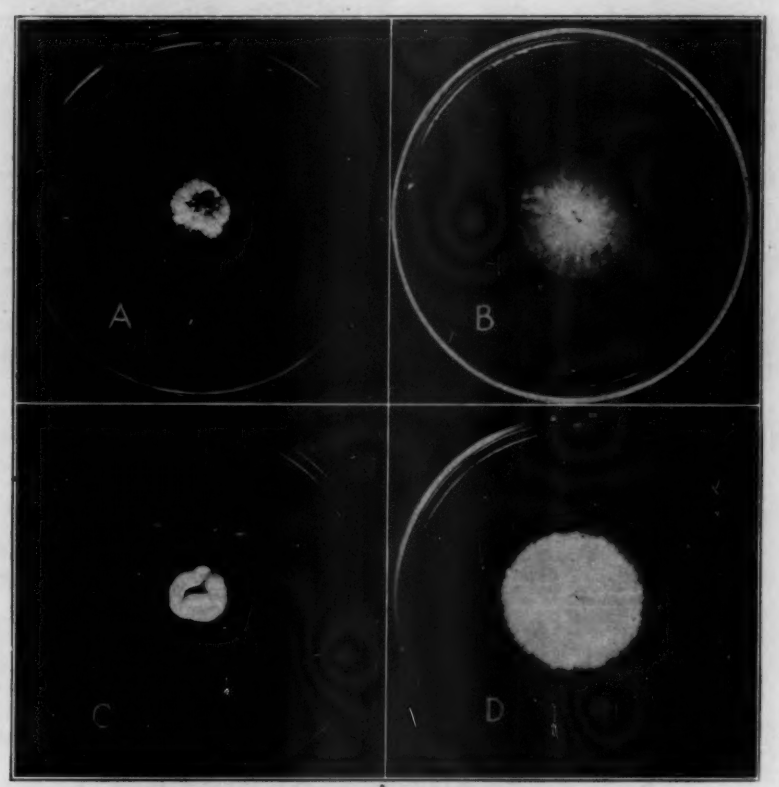

Fig. 5.—Trichophyton cultures on blood agar base ("difco") in forty-two days. *A*, T. album. *B*, T. discoides. *C*, T. album (blood agar base plus thiamine [0.1 mg. per hundred cubic centimeters]. *D*, T. discoides (blood agar base plus thiamine (0.1 mg. per hundred cubic centimeters).

Further studies on the cultural characteristics and requirements for growth of the organisms isolated in this series of cases are presented in a second paper.[17]

Inoculations with T. album and T. discoides obtained from the patients were unsuccessful in guinea pigs, but produced typical ringworm

17. Georg, L.: Growth Characteristics of the Faviform Trichophytons, to be published.

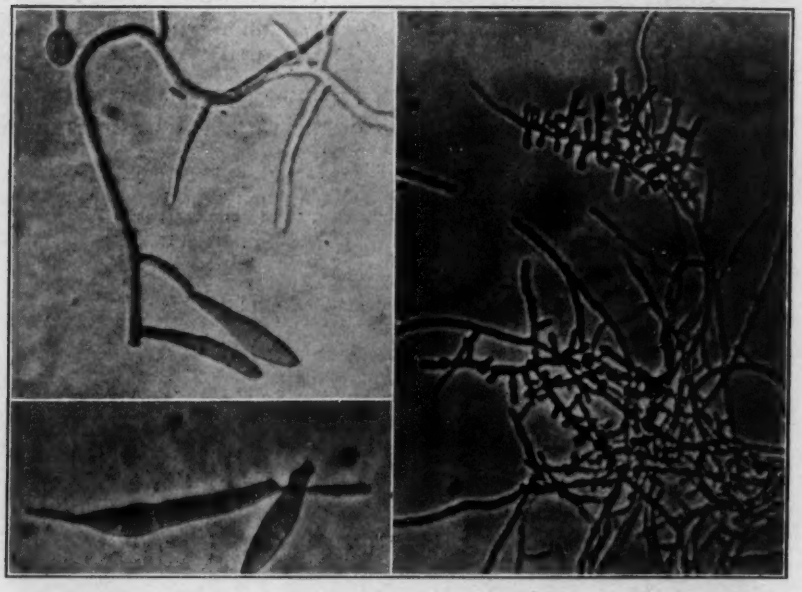

Fig. 6.—Microconidia and macroconidia formed on a blood agar base ("difco") enriched with thiamine. T. discoides.

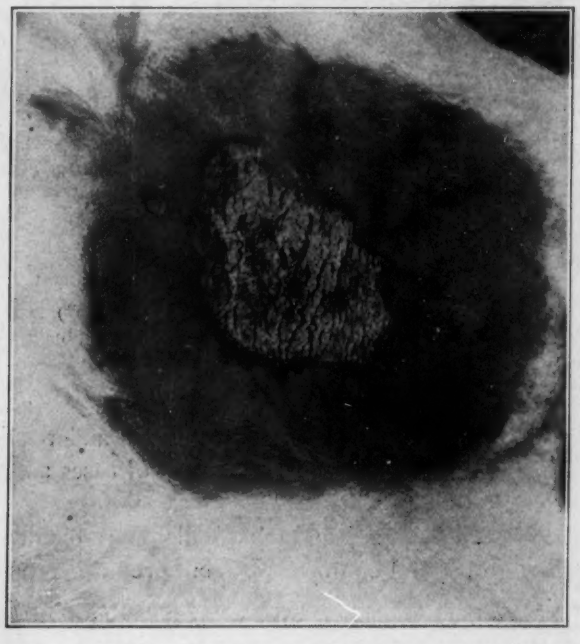

Fig. 7.—Lesion produced in rabbit twenty days after inoculation with T. album isolated from a patient in this series.

lesions in rabbits (fig. 7). The hairs showed ectothrix parasitism, and the scales were filled with chains of arthrospores. Pure cultures of T. album and T. discoides were obtained from the lesions in the rabbits.

SUMMARY

Twenty-three cases of deep suppurative ringworm infections contracted from cattle are reported. Descriptions of the lesions, their clinical course and the treatment used are given in detail. Examination of clinical material and cultural studies showed that in 14 cases the infection was caused by faviform trichophyta, in 12 cases by Trichophyton discoides and in 2 cases by Trichophyton album. Cultures in 4 cases yielded one of the gypseum trichophyta. Trichophyton mentagrophytes. In the remaining 5 cases in this series, pathogenic fungi were not observed on hairs, nor could they be grown in cultures. However, the nature of the lesions, the absence of bacterial infection and the history of contact with cattle infected with ringworm indicate that these cases were also of ringworm contracted from cattle. Blood agar base ("difco") enriched with thiamine is suggested as an isolation medium for use in cases of deep suppurative ringworm in which infection with the faviform trichophyta is suspected. Typical ringworm lesions were obtained in rabbits from inoculations with cultures of T. album and T. discoides from patients in this series, and pure cultures of the organisms were recovered.

Dr. Rhoda W. Benham of the Department of Dermatology, College of Physicians and Surgeons of Columbia University, gave guidance in the mycologic work.

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ACQUIRED LOOSE SKIN (CHALAZODERMA)

Report of a Case

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ABNORMALITIES in the distensibility and elasticity of the skin have been described for centuries under a variety of names. Considerable confusion has arisen in the nomenclature concerning diseases reported under such terms as cutis laxa, dermatolysis, cutis hyperelastica, cutis pendula, loose skin, dermatochalasis, pachydermatocele, chalazoderma, chalodermie, cutaneous geromorphism, dermatomegaly, lax skin, Ehlers-Danlos syndrome, elephantiasis and many others. These terms are loosely applied and tend to overlap in meaning.

In general, the aforenamed diseases can be separated fairly well into several groups:

1. Dermatolysis is the term first used by Alibert [1] in 1835 to describe hypertrophic disorders of the skin associated with laxness but without hyperelasticity. There seem to be two types (which may be related): first, generalized diffuse hypertrophy of the skin which hangs in heavy folds and is coarse and usually rough and, second, localized neurofibromatosis (von Recklinghausen's disease). Either may be congenital and may be associated with cutis verticis gyrata or similar diseases of the scalp. Alibert classified the disease into six subdivisions, dependent on the area affected. Sequeira,[2] Wise and Snyder,[3] Bielschowsky,[4] Rossi,[5] Umar,[6] Creite,[7] Vaglio [8] and Wigley [9] discussed cases belonging

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From the Department of Dermatology and Syphilology, University Hospitals, State University of Iowa, Iowa City.

1. Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928.

2. Sequeira, J. H.: Cutis pendula, Proc. Roy. Soc. Med. **9**:84, 1916.

3. Wise, F., and Snyder, E. J.: Diffuse and Disseminate Dermatolysis: Report of a Case, J. Cutan. Dis. **32**:139, 1914.

4. Bielschowsky, F.: Clinical Symptoms and Pathology of Circumscribed Lipatrophy (Cutis Laxa), Deutsches Arch. f. klin. Med. **166**:96, 1930.

5. Rossi, G.: On a Case of Concetti's Dermatomegaly (Cutis Laxa), Riv. di clin. pediat. **26**:137 (Feb. 25) 1928.

6. Umar, M.: A Case of Dermatolysis, Indian M. Gaz. **62**:208 (April) 1927.

7. Creite, O.: Zwei seltene Fälle von Missbildungen: I. Wampenbildung an Kopf, Hals, und Brust; II. Doppelseitige erbliche Quadratfüsse, Deutsche Ztschr. f. Chir. **197**:251, 1926.

(Footnotes continued on next page)

to this group. Sainz and Bravo [10] stated that these cases rightly belong in the group of nevoid disorders.

2. There are also described [11] other congenital cases which begin with generalized edema at birth, the edema being followed by diffuse dermatolysis. A biopsy in the case described by Raspi showed hypogenesis of the elastic tissue, laxness of the connective tissue bundles and a notable increase in the lymphatic network. Endocrine disturbances were postulated in these cases.

3. Cutis hyperelastica is the disease which van Meek'ren first described in 1682, and it has since been reported by many writers [12] under various terms. Frequently the extremely elastic skin is associated with hyperextensibility of the joints, deformities of the bones and a susceptibility of the skin to trauma; this group of dystrophies comprises the Ehlers-Danlos syndrome. Persons with this syndrome are the "india rubber men" of the circus. The syndrome seems to be inherited. Debré and his associates [13] reported a similar case, with osseous changes and hyperextensible joints and with looseness but relative inelasticity of the skin.

4. There is an acquired cutaneous disease, or group of diseases, in which local or generalized atrophy, laxness and inelasticity of the skin follow an inflammatory process. Sutton,[14] Fuhs [15] and Goodman and Traub [16] reported examples of the localized form, and in 1891 Souques

8. Vaglio, R.: Un caso di cutis laxa, Pediatria **31**:321 (March 15) 1923.

9. Wigley, J. E. M.: Dermatolysis (Cutis Laxa), Proc. Roy. Soc. Med. **36**:294 (April) 1943.

10. Sainz de Aja, E. A., and Bravo, J.: Unna-Jadassohn's Cutis Verticis Gyrata Compared with Alibert's Dermatolysis, Arch. Dermat. & Syph. **8**:797 (Dec.) 1923.

11. Negri, F.: A Case of "Cutis Laxa," Pediatria d. med. prat. **9**:106 (Feb.) 1934. Raspi, M.: On a Case of Cutis Laxa, Riv. di clin. pediat. **25**:648 (Sept.) 1927.

12. Comby, J.: Cutis laxa et syndrome d'Ehlers-Danlos, Arch. de méd. d. enf. **40**:107 (Feb.) 1937. Berggreen, P.: Zur Kenntnis der Erblichkeit der Cutis laxa (Gummihaut), Dermat. Wchnschr. **104**:374 (March 20) 1937. Benjamin, B., and Weiner, H.: Syndrome of Cutaneous Fragility and Hyperelasticity and Articular Hyperlaxity, Am. J. Dis. Child. **65**:247 (Feb.) 1943. Capurro, R.: Lax Skin, Hematoma, Cutaneous Atrophies, Muscular Hypotonia and Articular Laxity, Arch. latino-am. de pediat. **20**:713 (Nov.) 1926. Kalz, F.: Cutis laxa als Symptom allgemeiner Stützgewebswäche, Arch. f. Dermat. u. Syph. **171**:155, 1935.

13. Debré, R.; Marie, J., and Seringe, P.: "Cutis laxa" avec dystrophies osseuses, Bull. et. mém. Soc. méd. d. hôp. de Paris **53**:1038 (July 12) 1937.

14. Sutton, R.: Diseases of the Skin, ed. 8, St. Louis, C. V. Mosby Company, 1931.

15. Fuhs, H.: Ueber Dermatochalasis, Wien. klin. Wchnschr. **39**:1331 (Nov. 11) 1926.

16. Goodman, H., and Traub, E. F.: Dermatolysis, Surg., Gynec. & Obst. **42**:88 (Jan.) 1926.

and Charcot [17] described fully a remarkable case of generalized lax skin, cutaneous geromorphism, occurring in a girl of 11 within two months after an unusual systemic illness, characterized by fever, headache and abdominal pain followed by recurring papular eruptions "like mosquito bites." The skin became soft, loose and inelastic and hung in folds, especially at the neck, abdomen and about the roots of the extremities, giving her the appearance of extreme old age.

5. Chalazoderma is the classification into which the case herein reported falls. It differs from the last particularly by the absence of prodromal disease, inflammation or edema. In these cases the loose inelastic sagging skin is soft and thin, yet without superficial atrophic changes of old age. It occurs in young to middle-aged adults. Von Kétly [18] in 1901, under the name "chalodermie," reported a case of severe disease in a 30 year old woman who visited the clinic for a disorder of the respiratory tract. The cutaneous changes began at the age of 18, with sudden onset, and did not progress after a few months. The gluteal regions were most severely involved, and the skin in this area was likened to the "formless, ill-fitting, wide breeches of a Bosnian soldier." The breasts, which had been firm, hung lax and wide. Likewise, the skin of the abdomen and back was soft and loose and hung in pliable folds. In this case the face and neck were not involved, and over the back the thin skin allowed the bluish red vessels to show through. The patient showed no wasting of the muscles and no change in the skeletal structure and was in good health except for the infection of the respiratory tract, which healed in about two months. Weber [19] and Petges and Lecoullant,[20] in mentioning this case, stated that it was a hypertrophic disease related to neurofibromatosis (von Recklinghausen's disease). The photographs tend to suggest this, but the clinical description and the report of biopsy force one to consider the disease as one of those with destruction of the cutaneous supportive tissues. According to von Kétly the epidermis and upper part of the dermis were normal except for slightly increased pigment in the basal layer. The changes were limited to the deeper pars reticularis and the subcutis and consisted of edema with dilatation and thrombosis of the vessels, infiltration of young connective tissue cells and a decrease in number of collagenous and elastic bundles and with shredding and twisting of

17. Souques, A., and Charcot, J. B.: Géromorphism cutané, Nouv. Iconog. d. Salpétrière **4**:169, 1891.

18. von Kétly, L.: Ein Fall von eigenartiger Hautveränderung: "Chalodermie" (Schlaffhaut), Arch. f. Dermat. u. Syph. **56**:107, 1901.

19. Weber, F. P.: Chalasodermia or "Loose Skin" and Its Relationship to Subcutaneous Fibrous or Calcareous Nodules, etc., Urol. & Cutan. Rev. **27**:407 (July) **1923**.

20. Cited by Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936.

the collagenous fibers and granular degeneration and clumping of the elastic material.

In 1937 Goth [21] described a similar example, although of less severe disease, under the same name. His case occurred in a 23 year old woman who had been well until the age of 13, when she began to lose weight and dropped from 60 to 51 Kg. No explanation had been found, and she continued to be otherwise well until, at the age of 19, she suffered an attack of polyarthritis, beginning in the feet and spreading to the other joints. It apparently subsided without sequelae, but some time after this the skin changed, on the face becoming soft, pale and slightly brown and showing telangiectases, but no drooping or folding. On the arms and upper part of the thighs and over the scapulas and buttocks the skin was soft, pale, lax, thin and folded. Biopsy showed no change other than a paucity of elastic fibers, those remaining being frayed, disordered and clumped. No infiltrate was present. Goth points out that in these 2 cases there was no inflammation or edema of the skin prior to the onset of the disease and that although in 1 case there was a vascular element on the back and in the other on the face it was of different character than that seen in acrodermatitis atrophicans chronica. Ormsby and Montgomery [22] and Jadassohn [23] made cursory mention of cases of disease which may approximate the cases described as "chalodermie." Mraček,[24] in discussing blepharochalasis, described the same histologic changes demonstrated in our patient.

Also confusing the picture to a slight extent are the various forms of elephantiasis due to lymphangiomas and to chronic lymph stasis, as in Milroy's disease, elephantiasis nostras and filariasis.

Aside from Alibert's dermatolysis and cutis hyperelastica the literature is only sparsley provided with examples of these diseases, and many of those which do appear either are reported without photographs, biopsies or adequate descriptions or were reported many years ago, with the result that accurate delineation among them is impossible. Moreover, when there were prodromal signs or symptoms, they usually were not observed by the person reporting the case and cannot be evaluated.

REPORT OF A CASE

B. E. was first seen at the University Hospitals in September 1932, because of pelvic relaxation, and was admitted to the hospital for gynecologic surgical treatment, Her difficulty began in 1904 with the birth of her first child, and in 1907 a repair of further laceration suffered during her second delivery was

21. Goth, A.: Ueber Chalodermie (Kétly), Dermat. Wchnschr. **104**:426 (April 3), 1937.

22. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

23. Jadassohn, J.: Dermatologie, ed. 2, Vienna, Weidmann & Company, 1938.

24. Mraček, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1902.

necessary. A third delivery in 1916 broke down this repair, and increasing symptoms of pelvic pressure and backache ensued. Prolapse of the cervix through the vaginal orifice was noted in 1925. The general health had always been good. On physical examination a relaxed abdomen was noted, with many striae distensae; the uterus was poorly supported and there was an egg-sized cystocele, as well as a uterine fibroid, chronic cervicitis and cervical lacerations. The perineal support was good. No sign of the subsequent cutaneous deformity was observed. A vaginal hysterectomy and perineorrhaphy were performed, and the patient returned home after a convalescence prolonged by pelvic inflammation and pleuritis.

In December 1936 the patient returned to the hospital for admission to the department of ophthalmology, because of drooping of the eyelids. She stated that this had begun eighteen months previously and had been progressive to the point of obscuring her vision. The resulting entropion of the upper lids caused chronic conjunctivitis. There was mild ectropion of the lower lids. She denied any inflammation of the lids prior to or during these changes. The skin was soft and loose and gave the impression that the subcutaneous structures were gone. The redundant skin was resected from both eyelids, with a satisfactory result. The conjunctivitis improved, and the patient was discharged with a diagnosis of blepharochalasis. It is unforunate that no sections were made from the resected skin. The skin was still normal elsewhere.

In February 1937 she was readmitted, this time to the department of otolaryngology for treatment of chronic otitis media on the left side, which healed with conservative treatment. The blepharochalasis had progressed to some extent since the operation, but was satisfactorily controlled with the use of "scotch tape" to support the lids. There were still no changes in the skin other than that of the eyelids.

The patient was not seen again in this hospital until April 1942, when she returned to the department of obstetrics and gynecology for treatment for backache and cystocele. For the first time she showed the widely distributed changes in the supportive structures of the skin and was referred to the department of dermatology and syphilology for study. The patient stated that the cutaneous changes had been gradual and could not guess when the relaxation began to be evident in areas other than the lids, but it was presumably in 1937 or 1938.

Her general appearance was one of weakness and fatigue. The eyelids were supported by means of cellulose adhesive tape, but there was still entropion of the upper lids and ectropion of the lower ones. The forehead was deeply furrowed. The cheeks drooped, and the skin of the neck hung loosely, like a dewlap (fig., *A*). On the inner surface of the arms and on the contiguous part of the thorax the skin was also loose and folded (fig., *B*). Likewise, over the scapulas there were many soft thin folds. The breasts were lax and flaccid; the abdominal skin was flabby, and the skin of the buttocks, vulva and upper part of the thighs was loose and folded. The skin in all of the affected areas was fine, soft, inelastic and pale, without telangiectases, keratoses or other senile changes. The vaginal introitus was relaxed. Opinion of the gynecologists differed in respect to whether the pelvic relaxation was of the same nature as was usually seen, but a large cystocele and partial prolapse of the vault were noted. The general physical examination revealed no abnormalities except for moderate cardiac enlargement and blood pressure of 215 systolic and 100 diastolic. Neurologic examination revealed no sign of neurologic or muscular dystrophy. The patient was somewhat weaker than would be expected in a 57 year old woman. Quinine increased her weakness slightly, and neostigmine compound relieved it, but in the opinion of the consulting neurologist this was of no significance in respect to a diagnosis of myasthenia gravis, which had been suggested. The Wassermann reaction

of the blood was anticomplementary, but the reactions in Kahn and Kline tests were negative, these serologic observations being constant throughout her previous visits. The blood cell count and urinalysis revealed no abnormalities. A specimen for biopsy was taken from the skin of the right cheek. After an uneventful convalescence following anterior colporrhaphy and perineorrhaphy the patient returned home.

Microscopic examination of the biopsy section revealed thinning of the epidermis, with loss of the papillae. The hair and the sebaceous and sudoriferous

A, relaxation and drooping of the skin of the eyelids, cheeks and neck. The site of biopsy is visible on the right cheek. "Scotch tape" supports the right eyelid. *B*, drooping and formation of fine folds of skin on the posterior and lateral aspects of the thorax and inner surface of the arm. *C*, relaxation, sagging and folding of the skin of the vulva.

glands were normal. The tissues of the dermis appeared fragmented. Sections stained by Weigert's method showed loss of the elastic tissue in the pars papillaris, with advanced changes of the collagen to collastin. There was no normal elastic

tissue in the pars reticularis, the fibers being short and shredded and taking little stain. (It was impossible to be certain whether any of this was elastic tissue or whether it represented only degenerated collagenous tissue.) There was no disturbance of the elastic tissue in the sweat glands and vessels, and the subcutaneous fat was apparently normal.

In September 1942 the patient was called back to the hospital for further study. No noticeable change or progression had occurred in the cutaneous disease, and her other complaints had lessened. The physical examination revealed nothing new. Roentgenologic studies of the skull revealed no enlargement of the sella turcica and no other abnormalities. The basal metabolic rate was —10 per cent. Plastic procedures on the face were being considered, when pharyngitis developed and cultures of material from the throat grew virulent Klebs-Loeffler bacilli. She was transferred to the isolation wards, where the pharyngitis cleared quickly and without consequence, but the cultures remained positive. Thorough attempts to end her carrier status failed, and after five weeks she was returned home at her own request, in the custody of her county health officer. The patient has not returned to the hospital since that time.

This patient thus presents dystrophy of the connective tissues of the skin, probably associated with a similar disease of the pelvic supportive structures, progressive over a period of at least eight years, with abnormal looseness, inelasticity, drooping and folding of the skin of the eyelids, face, neck, thorax, abdomen, external genitals, arms and upper part of the thighs. The case fits well into the fifth group described, chalazoderma, and agrees in most respects, both clinically and microscopically, with the cases reported by von Kétly and Goth. Our patient, in contradistinction to theirs, showed the most decided changes about the face and neck and presented no telangiectases or other senile changes. Like theirs, there was no prodromal inflammation or edema and no hypertrophy either diffuse or in localized tumor masses.

SUMMARY

The literature on abnormalities in the distensibility of the skin is reviewed, and the types are classified into five groups on a basis of clinical and microscopic differences.

An unusual case of chalazoderma, fitting into the fifth group, is described.

ALLERGIC CONTACT DERMATITIS DUE TO WOOL FAT AND CHOLESTEROL

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THE PURPOSE of this report is to record 9 cases of contact dermatitis due to an oxycholesterol-petrolatum ointment base ("aquaphor") and related substances. Many cosmetic preparations contain wool fat and cholesterol, the active ingredient of wool fat. The sensitizing qualities of wool and wool fat are well known, but despite the widespread use of wool fat in many ointment bases and cosmetic creams there are few reports of dermatitis due to its use. The term allergic contact dermatitis is used in the title to differentiate this type of dermatitis from nonallergic contact dermatitis due to primary chemical or mechanical irritants.

In order to have the proper perspective, one should note that this article was written early in 1942, when sulfathiazole ointment had become popular and many articles were being published extolling its value. Only a few authors were reporting cases of contact dermatitis due to this drug, but soon severe allergic contact dermatitis due to local use of sulfathiazole was observed so frequently that the local use of this drug was condemned by many dermatologic societies.

REPORT OF CASES

CASE 1.—H. P., a white man aged 45, was first seen in October 1941, because of acute dermatitis of two days' duration on the face, neck, upper part of the chest and shoulders. The eruption consisted of confluent erythematous edematous dermatitis. The borders were made up of slightly infiltrated, erythematous plaques, varying in diameter from 1 to 3 cm. On the ankle there was a well defined, 4 by 8 cm., infiltrated and crusted plaque of one month's duration. It was surrounded by an ill defined zone of acute dermatitis of more recent origin. Compresses of diluted solution of aluminum acetate and phenol 0.4 cc., solution of aluminum acetate 6 cc., and "aquaphor" in sufficient quantity to make 60 Gm. were prescribed. After five days of this treatment the eruption was worse. Patch tests were made with the ointment containing "aquaphor," the pure (?) crystalline cholesterol (Boekringer & Son), the cholesterol supplied by the manufacturers of "aquaphor" (Duke Laboratories), "nivea creme," "tecto," anhydrous wool fat, the absorption base (Johns Hopkins Dispensary) and shaving cream (Parke, Davis & Company). Positive reactions were elicited to all of the substances. Patch tests with liquid petrolatum, olive oil, petrolatum, "qualatum" (Almay Pharmaceutical Corporation), several types of soaps and raw untreated wool, taken

directly from a sheep, elicited negative reactions. The patient had used 5 per cent sulfathiazole in "aquaphor" for chronic dermatitis on the ankle. The ointment caused acute dermatitis of the face and neck. In view of the tests the ointments containing "aquaphor" or wool fat were discontinued, and the eruption underwent involution in approximately one month.

Three years later the patient was retested with pure cholesterol, and a reaction of 3 plus was elicited.

CASE 2.—E. F., a white man aged 31, was first seen in October 1941. He complained of a chronic pruritic lichenoid eruption on the shins. It consisted of moderately well defined, dull red, conical papules with numerous excoriations and follicular pustules. He was treated with small doses of unfiltered roentgen rays, and 5 per cent sulfathiazole in "aquaphor" was prescribed. Five weeks later acute dermatitis was superimposed on the original eruption. Patch tests with the prescribed ointment gave a reaction of 3 plus. There were similar reactions to tests with cholesterols (Duke Laboratories), an absorption base (Johns Hopkins Dispensary formula) and anhydrous wool fat. Tests with "nivea creme" and "qualatum" produced weaker reactions. He was not sensitive to petrolatum. On November 27 his dermatitis was complicated by generalized

TABLE 1.—*Constituents of "Aquaphor" and Related Preparations*

Preparation	Alcohols and Esters of Cholesterols	Aliphatic Hydrocarbons	Water	Glycerin	Miscellaneous
"Aquaphor"	+	+			
"Tecto"	+	+	+	+	
"Nivea creme"	+	+	+	+	Perfume
"Nivea skin oil"	+	+	+	+	Perfume; sodium borate

furuncles. Sulfathiazole, 1 Gm. four times a day, was prescribed. On the following day a generalized morbilliform eruption developed. Use of the drug was then discontinued.

CASE 3.—L. C., a white woman aged 39, in January 1942 presented an eruption of one month's duration. It started in the retroauricular regions and then involved the face, neck, chest, back, axillas and scalp. The dermatitis was erythematovesicular and crusted. Patch tests showed that she was sensitive to nickel, 2.5 per cent sulfathiazole in "aquaphor," "tecto," "aquaphor," "nivea skin oil," cholesterol (Duke Laboratories), pure (?) cholesterol crystals and "Frederick's shampoo." Reactions were negative to tests with "pine oil soapless shampoo," "Vernon wave set," "qualatum" and a small piece of a woolen dress which she had worn at the time of the onset of the eruption. The patient had previously used the two shampoos, the wave set and the 2.5 per cent sulfathiazole ointment. The dermatitis was apparently due to the "Frederick shampoo" and was aggravated by the use of "aquaphor" containing sulfathiazole.

CASE 4.—E. H., a white woman aged 48, when first seen in January 1942 had had for three weeks an acute, weeping dermatitis on the face, neck, upper part of the chest, arms and hand. On other parts of the body the eruption consisted of discrete and confluent, erythematous, slightly scaly macules. The eruption disappeared after the use of compresses of solution of aluminum acetate and an emulsion of bentonite, water and olive oil. Reaction to patch tests with Barbara Gould "velvet of roses face cream" were strongly positive, and the reactions

to other tests with wool fat, "curex cream" and "Hind's deodorant" (containing aluminum sulfate) were negative. Approximately one month later an ointment containing "aquaphor" was prescribed. Within twenty-four hours after this salve was applied severe acute dermatitis developed on her face, neck and shoulders and on both surfaces of her forearms. Reactions to patch tests showed that she was sensitive to the "aquaphor" ointment, wool fat and cholesterol (Duke Laboratories), but not to "qualatum." The patient gave a history of previous ingestion of sulfathiazole, which had resulted in an eruption and fever.

CASE 5.—J. M., a white man aged 41, presented in September 1941 moderately active dermatophytosis of the feet. Equal parts of "aquaphor" and zinc oxide ointment were prescribed. He was not seen again for six weeks. When he returned there was extensive acute vesicular dermatitis of the feet and legs. Reactions to patch tests with the prescribed ointment, "nivea creme," "tecto," anhydrous wool fat, absorption base (Johns Hopkins Dispensary), cholesterol (Duke Labortories) and "aquaphor" were positive. Reactions to tests with "qualatum," liquid petrolatum and petrolatum were negative. He was given an ointment with "qualatum" as the vehicle. The dermatitis rapidly underwent involution, but relapsed. One month later the reaction to a patch test to "qualatum" was positive. The patient apparently had become sensitive to bases containing wool fat or its active principles, and later sensitivity to "qualatum" also developed.

CASE 6.—R. B., a white man aged 42, was first seen in 1933, complaining of chronic relapsing dermatitis on the left leg. For several years he had applied many ointments containing a wool fat or "aquaphor" base. In the fall of 1941 acute dermatitis developed in the treated area. He gave positive reactions to patch tests with "aquaphor," cholesterol (Duke Laboratories), "nivea creme" and anhydrous wool fat and negative reactions to tests with petrolatum and "qualatum."

CASE 7.—J. C., a white woman aged 38, in the fall of 1941 had applied to her feet a modified ointment of benzoic and salicylic acid in an "aquaphor" base. After several weeks acute dermatitis developed in the area of application. The reactions to patch tests were as follows: with the ointment 3 plus, "aquaphor" 2 plus, cholesterol (two occasions) 1 plus and anhydrous wool fat negative. Several years previously she had applied to her face a mild sulfur ointment with an "aquaphor" base. This had been discontinued, and when she attempted to use the ointment again acute dermatitis resulted.

CASE 8.—F. E., a white woman aged 33, complained of recurrent dermatitis of her hands. The history indicated that she might be sensitive to nickel, and a patch test with 5 per cent nickel sulfate applied for four hours elicited a strongly positive reaction. A reaction of 3 plus was obtained by patch tests with cholesterol (Duke Laboratories). "Qualatum" caused no reaction.

CASE 9.—M. J., a white woman aged 35, had had for four years cheilitis of undetermined cause on both lips. The lesion had failed to respond to numerous local and general therapeutic measures. The patient remarked that various ointments accentuated the cheilitis. In 1941 patch tests with "aquaphor," "nivea creme" "nivea skin oil" and anhydrous wool fat elicited a reaction of 2 plus and with "qualatum" a reaction of 1 plus. The reactions to repeated tests with cholesterol (Duke Laboratories) and with cholesterol crystals were negative. In April 1944 positive reactions were obtained in patch tests with "aquaphor."

COMMENT

Ramirez and Eller [1] reported the cases of 2 patients who were sensitive to wool fat. One was also sensitive to crude wool and wool extracts (?). Sulzberger and Morse [2] reported 2 patients who were sensitive to wool fat. One was a wool salesman, and the other patient was a dress designer. Hertslet [3] gave an example of a patient with a generalized eruption which resulted from the frequent handling of raw wool. The patient reacted positively to a patch test with wool fat. Milian and Garnier [4] described lichenoid dermatitis due to sensitivity to wool in a farmer who tended sheep. For three years the dermatitis had persisted on the legs and forearms. In discussing the farmer's case, Sézary wrote of 2 patients who were sensitive to wool fat as shown by patch tests. Sézary and Horowitz [5] stated that the active factor was isocholesterol. Cheilitis caused by lipstick was reported by Sézary,

TABLE 2.—*Reactions to Patch Tests*

Substances Used in Tests	Case Number								
	1	2	3	4	5	6	7	8	9
Ointment with "aquaphor" base	3+	3+	3+	3+	3+	2+	3+	...	...
"Aquaphor"	3+	2+	3+	...	3+	2+	2+	2+	2+
Cholesterol *	3+	3+	3+	3+	3+	3+	1+	2+	—
Cholesterol crystals †	3+	...	3+	...	...	...	...	...	—
"Nivea creme"	3+	3+	...	...	2+	2+	...	...	2+
"Tecto"	3+	...	2+	...	3	...	...	...	...
Anhydrous wool fat	2+	2+	...	3+	3+	2+	—	2+	2+
Absorption base ‡	3+	3+	...	...	2+	...	...	...	...
Petrolatum	—	—	...	...	—	—	...	—	...
"Qualatum" §	—	1+	—	—	2+	—	...	...	1+

* Duke Laboratories.
† Boekringer & Sons.
‡ Johns Hopkins Dispensary formula (contains cholesterol).
§ Almay Pharmaceutical Corporation.

Horowitz and Genet.[6] The patient was observed to be sensitive to wool fat and eosin. Fanburg [7] reported dermatitis due to "aquaphor" oint-

1. Ramirez, M. A., and Eller, J. J.: The "Patch" Test in "Contact Dermatitis" (Dermatitis Venenata), J. Allergy **1**:489, 1930.

2. Sulzberger, M. B., and Morse, J. L.: Hypersensitiveness to Wool Fat: Report of Two Cases, J. A. M. A. **96**:2099 (June 20) 1931.

3. Hertslet, L. E.: A Case of Allergic Dermatitis Due to Wool, South African M. J. **8**:182, 1934.

4. Milian, G., and Garnier, G.: Dermatose des tondeurs de moutons, Bull. Soc. franç. de dermat. et syph. **43**:1473, 1936.

5. Sézary, A., and Horowitz, A.: Intolérance cutanée à la lanoline, Bull. Soc. franç. de dermat. et syph. **43**:1544, 1936.

6. Sézary, A.; Horowitz, A., and Genet, H.: Cheilite du rouge (intolérance à l'éosine) chez une malade intolérante à la lanoline, Bull. Soc. franç. de dermat. et syph. **43**:1542, 1936.

7. Fanburg, S. J.: Dermatitis Due to Aquaphor: Report of a Case, Arch. Dermat. & Syph. **42**:479 (Sept.) 1940.

ment and discovered that the sensitivity was due to the cholesterol in "aquaphor," but the reaction to a patch test with hydrous wool fat, which also contained the cholesterol, was negative. In discussing the case of Fanburg's patient, Beerman stated that he had observed a patient who was known to be sensitive to wool in whom dermatitis appeared after the use of "nivea creme." Lord [8] reported 4 cases of cutaneous sensitization to wool: 2 patients had urticaria and 2 an allergic "eczema." None of the patients were sensitive to wool fat. In discussing industrial dermatitis due to wool fat Schwartz and Tulipan [9] described a dermatitis which started soon after occupational exposure to wool. It was an erythematous papulovesicular eruption on the back of the hands. The workman was extremely sensitive to wool. The eruption would clear if he remained away from work for a few days, but would return when he resumed his occupation. Cranch and his associates [10] were able to sensitize to wool fat 7 students in a group of 98 tested.

In 1938, Sulzberger and Goodman [11] described a case in which hypersensitivity to wool fat had developed and had presented an extremely difficult therapeutic problem. Sensitivity to this allergen was unrecognized for several years, and the chronic eruption on their patient's hands failed to improve until the exposure to topical remedies containing wool fat was stopped. Coca and his colleagues [12] listed wool fat as a sensitizer.

Since this report was written, in 1942, no additional cases of sensitivity to wool fat, "aquaphor" or cholesterol have come to my attention, in spite of the fact that I have occasionally used "aquaphor" or "nivea creme" as a base and frequently have prescribed "nivea skin oil" in the bath for generalized pruritus, bath dermatitis and related conditions. It is to be noted that 2 of the 9 patients who showed positive reactions to wool fat and cholesterol were observed to have retained their sensitivity to these substances when tested several years later. Three patients exhibited 3 plus reactions to "qualatum," but attempts were not made to find the exact sensitizing factor or factors.

The negative reactions to tests with cholesterol in case 9 are difficult to explain. The other 8 patients who were sensitive to "aquaphor"

8. Lord, L. W.: Cutaneous Sensitization to Wool, Arch. Dermat. & Syph. **26**:707 (Oct.) 1932.

9. Schwartz, L., and Tulipan, L.: Occupation Diseases of the Skin, Philadelphia, Lea & Febiger, 1939, p. 707.

10. Cranch, A. G.; Smyth, H. F., and Carpenter, C. P.: External Contact with Monethyl Ether of Diethylene Glycol (Carbitol Solvent), Arch. Dermat. & Syph. **45**:553 (March) 1942.

11. Sulzberger, M. B., and Goodman, J.: Allergy in Dermatology: A Critical Review of Recent Contributions, J. Allergy **9**:404, 1934.

12. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 386.

were also sensitive to cholesterol. The cholesterols are the active agents in the bases which permit the incorporation of water in "aquaphor" and wool fat.

SUMMARY

Nine patients who were sensitive to an oxycholesterol-petrolatum ointment base ("aquaphor") are reported. Eight of the patients were sensitive to cholesterol. The 9 patients also were sensitive to wool fat, "nivea creme" and related substances. Three patients were observed who exhibited reactions of 3 plus to patch tests with "quálatum." Five of the 9 patients had used a sulfathiazole ointment, and 2 had ingested sulfathiazole. In 3 of the patients a history of the therapeutic use of sulfathiazole was not obtained. Sulfathiazole may have acted as a sensitizer or may have had a synergistic sensitizing effect on the bases used in the ointment.

8 East Madison Street.

CUTANEOUS TESTING IN A CASE OF EXFOLIATIVE DERMATITIS CAUSED BY PENICILLIN

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DURHAM, N. C.
AND
JOSEPH TAMURA, Ph.D.
CINCINNATI

AS THE use of penicillin becomes more widespread and indiscriminate, reports of reactions of cutaneous sensitivity are increasing. Recent reports include those of Goldman, Friend and Mason,[1] and those of Gottschalk and Weiss.[2] The most severe cutaneous reaction, exfoliative dermatitis, was anticipated by Herrell,[3] and 1 case with cutaneous tests has been reported by Goldman and his co-workers.

Opportunity was afforded recently of studying another case of severe exfoliative dermatitis caused by penicillin. Because of the rarity of this reaction and the advanced age of the patient this case is presented.

REPORT OF A CASE

F. F., a 78 year old white man, was admitted to the Medical Service of the Cincinnati General Hospital on Feb. 27, 1946, acutely ill. Except for seasonal attacks of hay fever since childhood and one attack of cholecystitis in August 1945, he had been well until three days before hospitalization, when there was a sudden onset of pain in the right side accompanied with a chill and temperature of 104 F. Signs of consolidation in the lower lobe of the right lung were demonstrated on physical examination and by roentgenograms. Examination of the culture of the sputum showed the presence of type VII pneumococci. There was also a moderate degree of icterus. A diagnosis of lobar pneumonia and cholecystitis was made. Intramuscular administration of penicillin in a dosage of 20,000 units every three hours was instituted on Feb. 28, 1946. Several different com-

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Crystalline fractions were supplied by Bristol Laboratories, Inc.

This work was aided in part by a grant from Schenley Laboratories, Inc.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati and the Laboratory of Antibiotic Research, Cincinnati General Hospital; Joseph Tamura, director.

1. Goldman, L.; Friend, F., and Mason, L. M.: Eczematous Reactions to Penicillin with Report of Thirteen Cases, J. A. M. A. **131**:11 (July 13) 1946.

2. Gottschalk, H. R., and Weiss, R. S.: Epidermal Sensitivity to Penicillin, Arch. Dermat. & Syph. **53**:365-371 (April) 1946.

3. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1945.

mercial brands were used. The clinical course was uneventful until March 3, when a generalized erythematous maculopapular eruption was noted. Because of the extent of the pneumonic process and the age and general condition of the patient, penicillin therapy was not discontinued even though sensitivity to penicillin was suspected. The blood cell count showed the presence of 9,000 white cells and 4,800,000 red cells. Roentgenologic examination revealed "a definite decrease in the amount of previously described pneumonic infiltrate in the right side of the chest." In the following seventy-two hours, vesicles and blebs of various sizes were noted over the thighs, buttocks and abdomen. Rupture of these lesions left large denuded areas. Penicillin therapy was discontinued on March 6, when there was a generalized diffuse erythematous confluent vesicular eruption over the entire body, but most evident over the trunk and extremities. The face was moderately red, with some edema of the eyelids. There was also moderate pretibial edema and generalized lymphadenopathy. The mucous membranes of the mouth showed numerous areas of vesiculation and erosion. The patient was disoriented, and there were no elicitable complaints except of slight itching. Blood cell counts on March 6 showed 54,000 white cells, 94 per cent neutrophils and 6 per cent

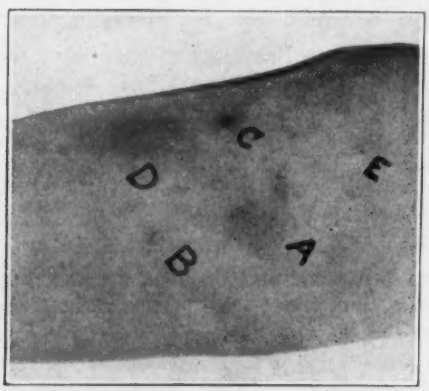

Fig. 1.—Reactions to intradermal tests, left forearm, forty-eight hour reading: *A*, crystalline sodium penicillin K; *B*, crude inactive penicillin; *C*, penicillin-penicillinase; *D*, stock solution of penicillin, and *E*, control (distilled water). Lymphangitic-like extensions at *A* and *D* are evident. The discoloration of the skin at *B* and *C* is due to pigment in the solution.

lymphocytes, with no evidence of eosinophilia. There followed a widespread exfoliation of the epidermis and loss of all the nails, but there was remarkably little alopecia. Convalescence was uneventful except for an entropion of the left lower eyelid. The dermatitis gradually receded over a period of four weeks. The pneumonic process gradually resolved, and the blood picture showed a gradual fall to normal in the white cell count. The patient was discharged from the hospital, free from symptoms of disease, on May 5. It was thought then that as a result of penicillin therapy he had had an eruption of a maculopapular type, which had developed into dermatitis exfoliativa because of the necessity of continuing penicillin therapy.

After the dermatitis had improved, many different types of cutaneous tests were made. Such tests may be grouped briefly under two general headings, intradermal (fig. 1) and contact. Both types of tests were employed because it had been demonstrated previously that persons who are sensitive to penicillin may reveal simultaneously the urticarial, tuberculin and eczematoid types of cutaneous response.

As has been reported before in cases of sensitivity to penicillin, this patient revealed both the urticarial and the tuberculin types of reaction. He did not show any urticarial reaction without a subsequent tuberculin type of reaction.

A biopsy, showing a reaction in seventy-two hours to the intradermal injection of 0.1 cc. of solution containing 200 units of penicillin, revealed definite areas of spongiosis, slight acanthosis and extensive edema of the pars papillaris, with a lymphocytic infiltrate which was perivascular in portions. Only an occasional eosinophil was noted. No giant cells or evidences of tuberculoid structure were observed. There were some fragmentation and separation of the collagen fibers.

TABLE 1.—*Intradermal Tests*

Material	Amount, Cc.	Concentration, Units	Result
Commercial penicillin A	0.1	1,000	+
Commercial penicillin B	0.1	1,000	+
Commercial penicillin B (autoclaved)	0.1	.....	—
Crystalline sodium penicillin K	0.1	.....	+
Sodium penicillin K (autoclaved)	0.1	.....	—
Commercial penicillin B (diluted)	0.1	200	+
		100	+
		25	+
		15	+
		2.5	+
		0.25	—
		0.025	—
Commercial penicillin B autoclaved (repeat)	0.1	.....	—
Commercial penicillin C (inactive)	0.1	.....	—
Commercial penicillin C and penicillinase	0.1	.....	—
Penicillin impurities (extract)	0.1	.....	+
Control (distilled water)	0.1	.....	—

TABLE 2.—*Patch Tests*

Material	Amount	Concentration, Units	Result
Commercial penicillin A	0.1 cc.	1,000	+
Crystalline sodium penicillin K	0.1 cc.	Approximately 1,000	+
Penicillin impurities	0.1 cc.	Approximately 100	+
Crude penicillin solution (inactive)	0.1 cc.	.....	—
Penicillin and penicillinase	0.1 cc.	.....	—
Penicillin ointment, 1,000 units per Gram	Approximately 5 Gm.	.....	+
Penicillin ointment base	Approximately 5 Gm.	.....	—
Crystalline sodium penicillin (autoclaved)	0.1 cc.	.....	—
Solution penicillin B autoclaved)	0.1 cc.	Approximately 1,000	—

From the data in table 1 it may be seen that this patient was sensitive also to the crystalline penicillin K. At the time of observation, no additional crystalline penicillin fractions were available for testing. An attempt was made to quantitate the reactions, and the end point was observed to be between 2.5 and 0.25 units. It was not possible to obtain closer values. Autoclaving was observed, on assay, to destroy over 90 per cent of the activity of penicillin, and autoclaved penicillin elicited negative reactions even when material was used which had a concentration prior to autoclaving of 0.1 cc. with 1,000 units. This was true of both the solution of commercial penicillin and the solution of crystalline penicillin.

One passive transfer study was made with blood serum by the Prausnitz-Küstner method, in which the donor sites were tested after twenty-four hours and again after five days. These results were negative.

In patch tests the patient was observed to be sensitive to crystalline K (fig. 2). The weak reaction to penicillin impurities may have been due to the penicillin still contained therein. Tests to determine the threshold of activity to penicillin mixtures or ointments were not successful. No patch tests were made at the donor sites of the Prausnitz-Küstner tests.

The patient was observed to exhibit no polyvalent sensitivity to trichophytin, gliotoxin or streptomycin.

Contact mucomembranous tests, after the method of Goldman and Goldman [4] and Goldman and Farrington,[5] were made with crystalline sodium penicillin K. The contact period was twenty-four hours, and the reaction was moderately positive. No conjunctival tests were made because of the presence of conjunctivitis and entropion.

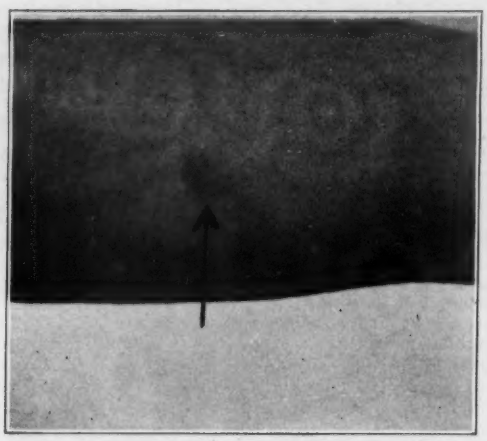

Fig. 2.—Reaction to patch test of right arm with crystalline sodium penicillin K; forty-eight hour reading.

TABLE 3.—*Cutaneous Tests with Additional Fungous Extracts*

Organism Extract	Intradermal Test	Patch Test
Trichophytin 1:30	+	—
Gliotoxin 0.2% and cetylpyridium chloride 0.2% in ointment base	Not done	—
Streptomycin	—	—

SUMMARY AND CONCLUSION

Severe dermatitis exfoliativa developed in a white man 78 years of age after parenteral treatment with penicillin for lobar pneumonia. A warning generalized maculopapular eruption first appeared, but continuation of penicillin therapy was necessitated by the severity of the pneu-

4. Goldman, L., and Goldman, B.: Contact Testing of Buccal Mucous Membrane for Stomatitis Venenata, Arch. Dermat. & Syph. **50**:79-84 (Aug.) 1944.

5. Goldman, L., and Farrington, J.: Contact Testing of the Buccal Mucous Membrane with Special Reference to Penicillin, Ann. Allergy **4**:6 (Nov.-Dec.) 1946.

monia, and the severe cutaneous reaction then developed. After the dermatitis cleared, extensive cutaneous tests were made. The patient was observed to exhibit urticarial and tuberculin types of reactions to different commercial brands of penicillin and to one sample of crystalline sodium penicillin K. Quantitative testing with graded dilutions revealed cessation of cutaneous response between 2.5 and 0.25 units. There was no response to autoclaved material, to crude inactive extracts or to penicillinase-inactivated extracts. No passive transfer reaction could be obtained. Results of patch tests indicated sensitivity to different types of commercial penicillin and to crystalline sodium K. No reactions were obtained with autoclaved material or with diluted mixtures. Tests with other extracts were made: patch tests with trichophytin, gliotoxin and streptomycin elicited negative results, while an intradermal test with trichophytin elicited positive results. This patient demonstrated that severe dermatitis exfoliativa can result from penicillin therapy.

Miss Ethel Barnett, A.B., technician for the Laboratory of Antibiotic Research of the Cincinnati General Hospital, gave technical assistance.

GRANULAR CELL MYOBLASTOMA

Report of Two Cases

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ABRIKOSSOFF [1] in 1926 described a group of peculiar tumors to which he gave the name myoblastic myoma. Other reports of this unusual type of growth followed, particularly in the European literature. Although the location of the majority of lesions which have been reported places them in the province of dermatologists, American dermatologic literature contains, at the time of writing only one paper on the subject, that of Tuta and Schmidt,[2] and the only dermatologic textbook mentioning this form of myoblastic growth is that of Ormsby and Montgomery.[3]

Klemperer [4] in 1934 thoroughly reviewed the literature on this subject and reported 44 cases, including 6 of his own. These tumors occurred in all parts of the body. In 1937 Gray and Gruenfeld [5] summarized the literature of 77 cases and added 5 others having the characteristics of myoblastoma. In 1942 Iglauer [6] reported 3 cases of myoblastoma of the larynx, and in 1943 Altman [7] added 3 more cases of this type of tumor occurring in the external auditory canal. Horn and

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From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Abrikossoff, A. I.: Ueber Myome ausgehend von der quergestreiften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215, 1926.

2. Tuta, J. A., and Schmidt, F. R.: So-Called Myoblastoma: Report of Three Cases of Myoblastoma of the Skin and One Case of Myoblastoma of the Trapezius Muscle, Arch. Dermat. & Syph. **46**:225 (Aug.) 1942.

3. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 803.

4. Klemperer, P.: Myoblastoma of the Striated Muscle, Am. J. Cancer **20**:324, 1934.

5. Gray, S. H., and Gruenfeld, G. E.: Myoblastoma, Am. J. Cancer **30**:699, 1937.

6. Iglauer, S.: Myoblastoma of Larynx, Ann. Otol., Rhin. & Laryng. **51**:1089, 1942.

7. Altman, F.: Granular Cell Myoblastomas of External Auditory Meatus, Laryngoscope **53**:195, 1943.

Stout [8] in 1943 brought the literature to date with 120 cases and suggested that the tumor be called granular cell myoblastoma, since this term describes the characteristic type of cell of this benign tumor. Crane and Tremblay [9] in 1945 reviewed all the reported cases of myoblastoma and were able to collect the details of 162 cases, including 5 of their own. This thorough and exhaustive summary brings to date all the known cases of myoblastoma, variously described as myoblastic myoma, rhabdomyoma of peculiar cell type, myoblastoma, granular cell myoblastoma and *rhabdomyome granulo-cellulaire*.

We feel that reports of myoblastoma should be added to the American dermatologic literature for several reasons: First, accumulating reports show that it is a not uncommon type of tumor; second, it occurs chiefly in the tongue, skin and mucous membranes; third, although it is doubtless seen by dermatologists, the dermatologic literature is lacking in reports of these cases, and finally, it is important from the viewpoint of differential diagnosis. We shall therefore review the subject briefly and report 2 additional cases.

Striated muscle cell tumors are of two types: one is derived from the adult striated muscle cell and is designated rhabdomyoma, and the other stems from the juvenile muscle cells, or embryonic myoblast, and is called myoblastoma. Abrikossoff felt that the tumor cells were juvenile muscle cells which developed during the process of repair and regeneration following trauma to the striated muscle fibers. Some believe that the cells observed in this tumor are striated muscle fibers which have lost their transverse and longitudinal striations and have become transformed or degenerated into cells of granular cytoplasm. These cells then take on neoplastic qualities. Others feel that the presence of these cells in a part not ordinarily containing muscle tissue is against the theory of degeneration, and they favor the neoplastic formation. These followers suggest that the granular cell myoblastomas may arise from embryonal rests of aberrant myoblastic tissue in places where striated muscle is not normally present. Many writers agree that these cells are of myogenous origin, namely, from primitive myoblasts. They base their opinions on the observation of cross and longitudinal striations within the granular cells or transitions between granular cells and striated muscle fibers. Klemperer [4] described in 1 of his cases an arrangement of granules in transverse rows, suggestive of striations. Horn and Stout,[8] Crane and Tremblay,[9] Thoma [10] and Diss [11] also observed

8. Horn, R. C., Jr., and Stout, A. P.: Granular Cell Myoblastoma, Surg., Gynec. & Obst. **76**:315, 1943.

9. Crane, A. R., and Tremblay, R. G.: Myoblastoma, Am. J. Path. **21**:357, 1945.

10. Thoma, K. H.: Rhabdomyoma of Tongue, Am. J. Orthodontics (Oral Surg. Sect.) **27**:235, 1941.

11. Diss, A.: Le rhabdomyome granulo-cellulaire de la langue, Ann. d'anat. path. **7**:1071, 1930.

longitudinal striations, suggestive of myofibrils, and parallel cross striations in isolated granular cells. The last word has not been spoken regarding the origin of these tumors, but some day this may be clarified to the satisfaction of all.

Granular cell myoblastomas are commonest between the ages of 30 and 50, although they may occur at any age. Males and females are equally affected. The tumors usually appear as pea-sized nontender nodules, varying from 1 to 2 cm. or larger in diameter. They are discrete rounded or nodular firm masses which protrude from the surface and are pinkish to yellowish. Clinically myoblastoma cannot be differentiated from xanthoma or fibroma, but histologically it is a distinct entity.

Microscopically, the characteristic cells are large, pale and polyhedral, containing acidophilic granular cytoplasm. They vary from 20 to 60 microns in diameter, and even larger ones have been reported. The nuclei are small, round or oval and somewhat vesicular. At times more than one nucleus are present. The nuclei are usually placed centrally, and in some instances nucleoli have been observed. At times ribbon-like or irregular syncytial masses may occur. Alveloar arrangement of some of the cells has also been noted. Hartz [12] presented a case in which the organoid pattern of growth was entirely present. The neoplastic elements stand out from the surrounding muscle because of their lighter color and pale-staining cells. The cells are surrounded by delicate strands of connective tissue fibrils. Sudan and other fat stains reveal no fat, distinguishing them from the foam cells of xanthoma. Some of the tumors are definitely encapsulated. In some cases, the capsule is absent and the cells blend with the adjacent muscle fibers.

Myoblastomas are generally benign tumors. This has been confirmed by most observers. Many of these tumors which have been reported as showing evidence of malignancy are thought to be rhabdomyosarcomas. Ravich, Stout and Ravich [13] did report a granular cell myoblastoma of the urinary bladder which became malignant and metastasized, but this occurrence is an exception rather than the rule.

After removal of some of these tumors, local recurrences have been noted. This is caused by the lack of encapsulation, as a result of which tumor cells infiltrate between the striated muscle fibers. Myoblastomas should therefore be excised with a fair margin of safety, and then a biopsy should be made. Histologic examination will determine the type of tumor and whether it has been removed in its entirety. That a single nonulcerated lesion on the tongue or skin is benign is usually

12. Hartz, P. H.: So-Called Granular Cell Myoblastoma of Thigh with Organoid Structure, Am. J. Clin. Path. **14**:582, 1944.

13. Ravich, A.; Stout, A. P., and Ravich, R. A.: Malignant Granular Cell Myoblastoma Involving the Urinary Bladder, Ann. Surg. **121**:361, 1945.

taken for granted. However, when there is a recurrence one begins to wonder whether a mistake in diagnosis has been made. This can usually be clarified by histologic examination.

One should also be aware of the fact that when these growths occur in the skin and beneath the mucosal surfaces, a proliferation of squamous epithelium occurs. The epithelium covering these areas at times will present epithelioma-like proliferative changes, and, as a result, squamous cell epithelioma has been erroneously diagnosed. This, too, can be prevented by a histologic examination of the tissue. We strongly urge biopsies of lesions of the tongue, especially when there is a recurrence after removal of what appeared to be a benign lesion.

Myoblastomas have a predilection for the proximal part of the alimentary tract and upper respiratory tract. The tongue is the com-

Summary of Cases of Myoblastoma Reported in the Literature

Site	Number
Tongue	62*
Skin	18*
Subcutis	17
Muscle	13
Maxilla	11
Larynx and vocal cords	8
Breast	8
Mandible	6
Lip	4
Ear	3
Trachea and bronchi	3
Alveolar process	2
Others	9
Total	164

* This includes our case.

monest site for these tumors, although they have been found widely distributed throughout the body. Of 164 cases recorded (including the 2 about to be reported), in 62 the myoblastomas were located in the tongue. The skin and subcutis are the next most frequent sites. Crane and Tremblay tabulated the site of occurrence as listed in the accompanying table.

CASE 1.—M. M., a man aged 44, born in the United States, first noticed a small lump on the right side of his tongue about a year previous to examination. The lesion grew slowly, but there were no subjective symptoms other than the feeling of a mass. Examination revealed a small oval tumor on the anterior dorsal surface of the tongue near the right border, measuring about 0.75 cm. in its longest diameter. The color was that of normal mucous membrane or perhaps slightly paler. The papillae were absent over the tumor. There was no adenopathy or interference with mastication, and no changes in sensation were manifested. The tissues surrounding the lesion were anesthetized with procaine hydrochloride, and with the cutting current of the high frequency machine the tumor was excised in toto. The base of the wound was electrodesiccated.

Microscopic examination of the specimen showed the epithelium to be that of mucous membrane, with no granular layer present. Tumor cells were seen beneath the epithelium, extending downward between the muscle fibers. The cells were large and pale staining, with granular cytoplasm and a well defined cell membrane. One or more nuclei were present in each cell. With high power magnification, the large round and polygonal cells could be clearly seen. They varied from 20 to 60 microns in size. The cells were clearly outlined, and the cytoplasm was com-

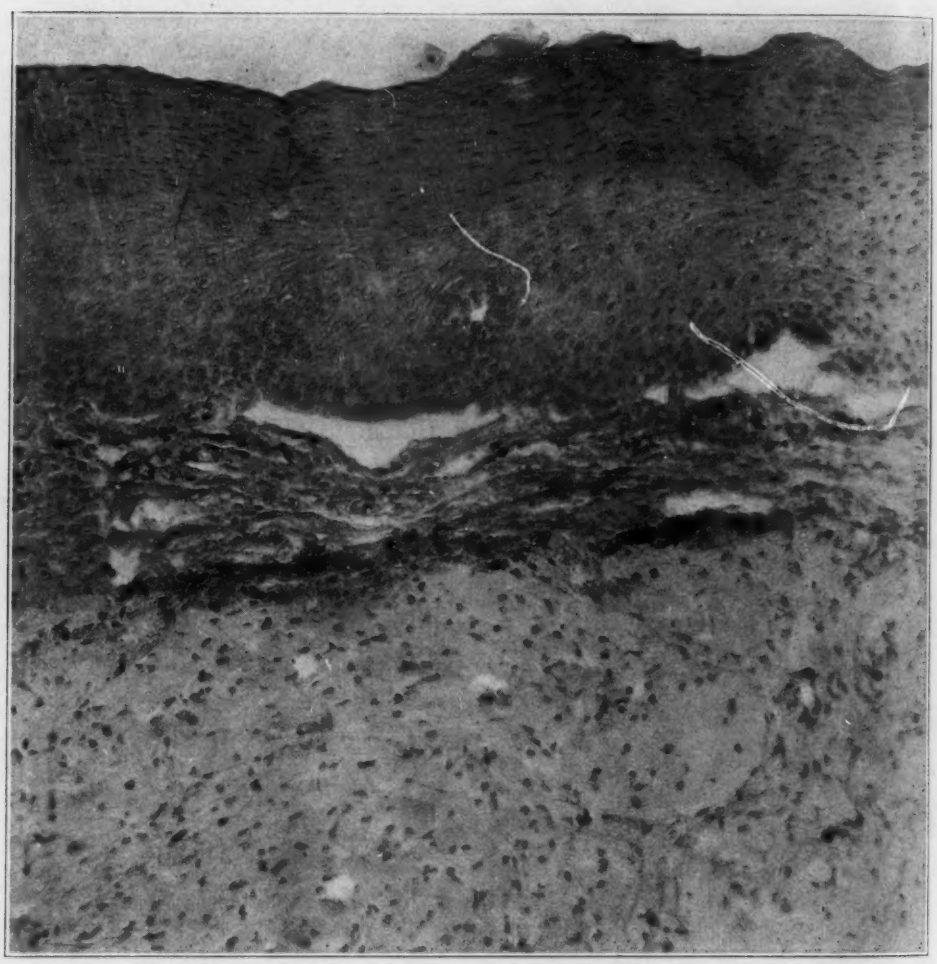

Fig. 1.—The surface of the mucous memebrane overlying the tumor is essentially normal. The tumor cells are pale staining, large, oval or round and contain one to several nuclei (hemotoxylin and eosin stain: × 175).

posed of densely packed granules, without definite arrangement. In each cell was a round or angular nucleus of a vesicular nature; some cells contained more than one nucleus, and some nuclei contained more than one nucleolus. A fine network of connective tissue fibers surrounded these large cells. These observations are consistent with those of granular cell myoblastoma.

CASE 2.—I. W.,[14] a man aged 40, came to the Skin and Cancer Unit on March 19, 1946, complaining of a nodule, about the size of a marble, on the dorsum of the index finger of the right hand. Clinically it appeared to be a neurofibroma. The nodule was excised and sent to the laboratory for examination.

Dr. Charles Sims reported that the epidermis revealed no noteworthy characteristics. Throughout the upper, middle and deep layers of the corium were

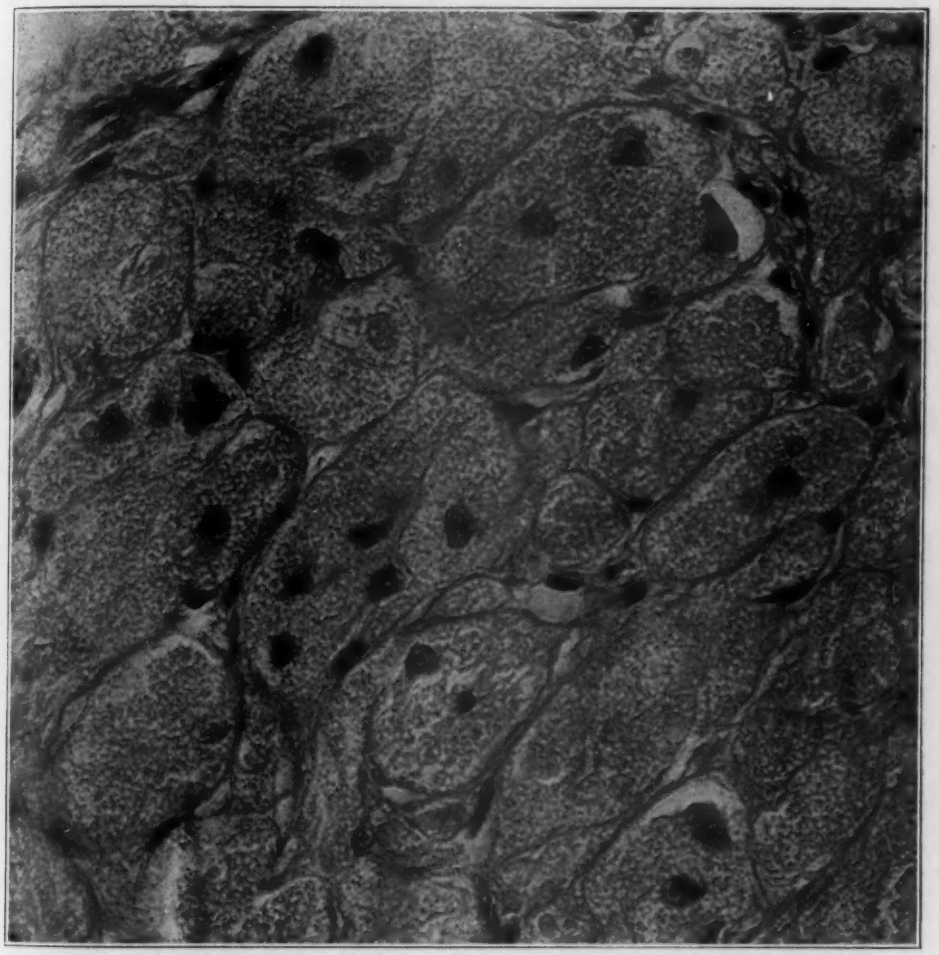

Fig. 2.—Typical tumor cells, showing one to several nuclei in each cell, the granular appearance of the cytoplasm and the distinct cellular outlines. The cells are separated from one another by fine connective tissue fibrils (hematoxylin and eosin stain: × 375).

numerous cellular masses of varying sizes and shapes, which stained a little paler than the surrounding normal collagen. These masses were apparently present in

14. Permission was granted to report this case from the service of Max Scheer, M.D., Skin and Cancer Unit, Post-Graduate Medical School and Hospital.

the interstitial lymphatic spaces. Examined under high power magnification they were apparently composed of well defined and rather large cells, some larger than others, containing a large round or oval vesicular nucleus and granular cytoplasm. Other inflammatory cells were not present to any degree. In one or two instances, multinucleated cells could be observed. No muscle was seen in this section. With the Van Gieson stain the granular cells were yellowish, in contrast to the surrounding collagen, which was pink. (Dr. M. Richter and Dr. W. Sachs helped to interpret the slides.)

SUMMARY

The literature on myoblastoma is briefly reviewed, and the genesis and histologic structure of this type of striated muscle cell tumor are discussed. The locations of the reported cases are tabulated, and 2 additional cases are described.

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CHEMISTRY OF PALMAR SWEAT

III. Reducing Substances (Glucose)

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OUR PREVIOUS studies on the chemistry of palmar sweat, collected from the openings of the sweat ducts of the finger tips of normal subjects,[1] indicated that both chloride[2] and urea[3] are more concentrated in the sweat when the sweat gland is functioning intermittently than when it is functioning continuously.

This report deals with similar studies on the concentration of glucose in palmar sweat, or rather of reducing substances in the sweat, since the analytic method[4] used is not specific for glucose alone.

There are conflicting reports[5] in the literature regarding the concentration of sugar in the sweat as well as regarding its presence or

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From the Section on Dermatology and Syphilology (Dr. Lobitz), and the Division of Clinical Biochemistry (Dr. Osterberg), Mayo Clinic.

1. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: Preliminary Report; Apparatus and Technics, J. Invest. Dermat. **6**:63-73 (Feb.) 1945.

2. Lobitz, W. C., jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: II. Chloride, Arch. Dermat. & Syph. **56**:462-467 (Oct.) 1947.

3. Lobitz, W. C., Jr., and Osteberg, A. E.: Chemistry of Palmar Sweat: IV. Urea. Arch. Dermat. & Syph., this issue, p. 827.

4. Walker, A. M., and Reisinger, J. A.: Quantitative Studies of the Composition of Glomerular Urine: IX. The Concentration of Reducing Substances in Glomerular Urine from Frogs and Necturi Determined by Ultramicro-Adaptation of the Method of Sumner; Observations on the Action of Phlorhizin, J. Biol. Chem. **101**:223-237 (June) 1933.

5. (*a*) Usher, B., and Rabinowitch, I. M.: Excretion of Sugar in Sweat: Its Relationship to Eczema, Arch. Dermat. & Syph. **16**:706-713 (Dec.) 1927. (*b*) McSwiney, B. A.: The Composition of Human Perspiration, Proc. Roy. Soc. Med. **27**:839-848 (May) 1934. (*c*) Silvers, S.; Forster, W., and Talbert, G. A.: Simultaneous Study of the Constituents of the Sweat, Urine and Blood, Also Gastric Acidity and Other Manifestations Resulting from Sweating: VI. Sugar, Am. J. Physiol. **84**:577-582 (April) 1928. (*d*) Schulze, W., and Kunz, K.: Ueber den Anteil des als Osazon bestimmten Zuckers und einiger anderer Substanzen am Reduktionsvermögen des Schweisses, Arch. f. Dermat. u. Syph. **181**:

(Footnote continued on next page)

absence in the sweat in normal states and in disease. All previous studies of this type have been carried out on general body, or thermal-regulating, sweat. The variations in the reports seem dependent in part on the method of collection of sweat, the manner of handling the sweat after collection and the analytic method used. This fact is illustrated, each from a different approach, by several authors: Usher and Rabinowitch [5a] stated that there are appreciable differences in the content of sugar of general body sweat containing epithelial debris and so forth before and after the sweat is cleared with kaolin. McSwiney [5b] observed that the action of bacteria present in the sweat decreased the concentration of sugar in the sweat. Silvers, Forster and Talbert,[5c] Schulze and Kunz [5d] and Schulze [5e] showed variations in the concentration of sugar in the sweat when different analytic methods were used. The values for sugar reported for general body, or thermal-regulating, sweat vary from 0 to 40 mg. of glucose per hundred cubic centimeters of sweat.[5] Schulze and Kunz showed that although reducing substances are measurable in sweat, when the sugar is determined as osazone there is no glucose present.

It seems agreed, with one exception,[5h] that there is no relation between sugar in the blood and sugar in the sweat in normal subjects whose blood sugar has been elevated nor in subjects with elevated levels of blood sugar resulting from diabetes mellitus.[6]

In our studies on palmar sweat the method of collection [1] is such that only pure sweat, uncontaminated by epithelial cells, oils and so forth, is obtained. The procedure of collection and analysis for this study is the same as that used in the study on urea,[3] that is, whenever possible we collected two separate specimens of sweat from the same subject during the half-hour period of collection. At the end of the period specimens of blood and urine were obtained. The volumes of sweat were measured by the manipulative technic of Richards, Bordley

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486-494 (Dec.) 1940. (*e*) Schulze, W.: Ueber den "Zucker" gehalt auf der Haut, im Hautdialysat und im Schweiss, ibid. **181**:471-485 (Dec.) 1940. (*f*) Usher, B.: Human Sweat as Culture Medium for Bacteria: Preliminary Report, Arch. Dermat. & Syph. **18**:276-280 (Aug.) 1928. (*g*) Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, J. Biol. Chem. **99**:781-790 (Feb.) 1933. (*h*) Marchionini, A., and Ottenstein, B.: Stoffwechselveränderungen im Schwitzbad bei Hautgesunden und Hautkranken: II. Einfluss auf den Kohlehydrate- und Lipoidstoffwechsel. Klin. Wchnschr. **10**:971-973 (May 23) 1931. (*i*) Williams, J. W.: The Pathological Physiology of the Kidneys (and Sweat Glands) in Infections, Urol. & Cutan. Rev. **44**:47-49 (Jan.) 1940. (*j*) Ito, S.: Significance of Blood Sugar During Sweat Secretion in Man, J. Orient. Med. (Abstr. Sect.) **28**:61 (April) 1938.

6. Usher and Rabinowitch.[5a] Silvers, Forster and Talbert.[5c] Schulze.[5e]

and Walker.[7] The analyses for reducing substances in the palmar sweat were made by the capillary tube colorimetry method of Walker and Reisinger[4] (using dinitrosalicylic acid reagent, Sumner's method), which was recently adapted by us[8] to the spectrophotometer. The estimations of glucose in the blood were made by the method of Folin and Wu.[9] The urine was tested qualitatively for the presence of reducing substances by Benedict's qualitative copper sulfate solution.

Five normal men and 5 normal women between the ages of 22 and 35 years were studied. From this group a total of forty-seven successful collections and analyses of palmar sweat were made (table 1). Nineteen of the collections (from 4 men and 3 women) were of the so-called profuse physiologic type, in which the sweat gland was working continuously as in thermal-regulating sweat. Twenty-eight collections (5 men and 3 women) were of the so-called intermittent physiologic type, in which the sweat droplets appeared at the openings of the sweat duct intermittently and the sweat gland apparently rested during the intervals between such work. In seven instances we were able to obtain both physiologic types of palmar sweating, separately from the same subject and during a single half-hour period of collection. In no instance was there any consistent significant difference in the concentration of reducing substances in the two different physiologic types of palmar sweat. The mean value for reducing substances in "profuse" sweat was 3.08 mg. of glucose per hundred cubic centimeters (maximum 11 mg. and minimum 0), the median was 2.6 mg. of glucose per hundred cubic centimeters and the mode 0. The intermittent type of sweat gave a mean value of 2.86 mg. of glucose per hundred cubic centimeters (maximum 16 mg. and minimum 0), a median of 0 and a mode of 0. The levels for glucose in the blood were normal with a mean of 86 mg. per hundred cubic centimeters (maximum 100, minimum 74). All specimens of urine yielded a negative reaction in qualitative tests for reducing substances.

From these studies it would seem that the sugar barrier in the palmar sweat gland is most efficient at normal levels of sugar in the blood. These values for reducing substances are lower than the average

7. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine: VII. Manipulative Technique of Capillary Tube Colorimetry, J. Biol. Chem. **101**:179-191 (June) 1933.

8. Lobitz, W. C., Jr., and Osterberg, A. E.: The Use of the Spectrophotometer in Capillary Tube Colorimetry for the Determination of Reducing Substances (Glucose), Chlorides, Ammonia Nitrogen, Uric Acid, and Creatinine, J. Invest. Dermat. **7**:135-144 (June) 1946.

9. Folin, O., and Wu, H.: A System of Blood Analysis: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367-374 (March 20) 1920.

values for general body, or thermal-regulating, sweat reported in the literature and agree more closely with values on general body sweat reported by Schulze [5e] and Schulze and Kunz.[5d]

TABLE 1.—*Reducing Substances in Blood and Palmar Sweat of Normal Persons**

Subject	Age, Years	Sex	Month, Day, 1945	Physiologic Type of Sweating	Volume of Sweat, in 0.35 Mm.† Tube, per Minute from 50 Glands, Mm.	Volume of Urine per Minute, Cc.	Reducing Substances (Glucose), Mg. per 100 Cc.	
							Palmar Sweat	Blood
R. C.	25	F	11/28	Profuse	0.49	0.25	6.4	86
				Profuse	1.02	....	8.8	..
			11/29	Profuse	1.98	0.31	2.0	78
				Profuse	2.04	....	2.0	..
			11/30	Profuse	1.15	0.32	2.0	95
				Profuse	0.33	....	2.7	..
D. M.	22	F	11/28	Intermittent	0.19	0.30	6.4	84
				Profuse	0.56	....	3.8	..
			11/29	Profuse	0.78	0.34	2.0	86
				Intermittent	0.08	....	12.0	..
			11/30	Intermittent	0.13	0.31	16.0	86
				Intermittent	0.10	....	5.3	..
J. M.	22	F	12/ 1	Intermittent	0.10	0.25	0.0	90
			12/ 3	Intermittent	0.03	0.43	3.0	95
			12/ 5	Intermittent	0.08	0.85	0.0	83
				Intermittent	0.03	....	0.0	..
G. S.	27	M	12/ 3	Intermittent	0.09	1.37	13.0	86
				Profuse	0.66	....	4.0	..
			12/ 4	Intermittent	0.08	0.87	0.0	83
			12/13	Intermittent	0.24	1.28	0.0	83
				Profuse	0.25	....	2.6	..
E. W.	35	F	12/ 4	Intermittent	0.08	0.66	0.0	90
				Intermittent	0.12	....	0.0	..
			12/ 5	Intermittent	0.04	0.70	0.0	86
			12/10	Intermittent	0.71	0.60	0.0	88
R. M.	28	M	12/ 5	Intermittent	0.05	0.53	0.0	83
				Intermittent	0.08	....	0.0	..
			12/11	Intermittent	0.17	1.00	0.0	95
				Intermittent	0.13	....	0.0	..
			12/12	Profuse	0.37	1.20	0.0	90
				Intermittent	0.13	....	0.0	..
P. C.	34	M	12/ 8	Profuse	0.05	0.26	11.0	83
				Intermittent	0.03	....	0.0	..
			12/10	Intermittent	0.03	0.40	0.0	74
			12/11	Intermittent	0.07	0.65	9.4	83
G. N.	27	F	12/14	Profuse	0.3	4.6	3.6	74
			12/15	Profuse	0.85	4.4	0.0	74
				Profuse	0.48	....	3.2	..
			12/17	Profuse	0.31	5.1	0.0	83
U. S.	32	M	12/13	Intermittent	0.05	0.50	0.0	74
			12/14	Intermittent	0.03	0.44	0.0	100
			12/17	Intermittent	0.01	0.77	0.0	83
H. T.	28	M	11/28	Profuse	0.54	0.60	4.5	95
				Intermittent	0.13	....	10.0	..
			11/29	Intermittent	0.17	0.80	5.0	95
			12/18	Profuse	0.25	1.10	0.0	95
				Profuse	0.16	1.10	0.0	..

* All specimens of urine yielded a negative reaction for glucose with Benedict's qualitative solution.
† Inside diameter.

In order to raise the levels of sugar in the blood in normal subjects we fed 100 Gm. of glucose by mouth on three occasions to subjects (2 women, D. M. and G. N.) who were known to be able to deliver

profuse dilute palmar sweat on request. Specimens of blood and urine were collected at the same time (table 2). There was no spilling of glucose into the sweat in any of the specimens. The peak values for reducing substances in the blood were 168, 139 and 111 mg. per hundred cubic centimeters. The specimens of urine were negative for glucose by qualitative test.

To learn whether the sugar barrier in the palmar sweat gland was efficient at even higher levels of sugar in the blood we next gave 20 Gm. of glucose (20 per cent solution) intravenously to 3 normal men and

TABLE 2.—*Reducing Substances in Blood, Sweat and Urine Before and After Oral Administration of Glucose*

Subject	Age, Years	Sex	Time After Oral Administration of Glucose		Reducing Substances (Glucose), Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
			Hours	Minutes	Blood	Palmar Sweat *	
			Fasting Values				
D. M.....	22	F	..	..	86	0	—
			After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)				
			0	45	149	0	—
			1	20	168	0	—
			1	50	153	0	—
			Fasting Values				
D. M.....	22	F	..	..	95	0	—
			After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)				
			0	35	139	0	—
			1	10	107	0	—
			Fasting Values				
G. N.....	27	F	..	..	86	0	—
			After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)				
			0	40	111	0	—
			1	30	74	0	—
			2	15	82	0	—

* All specimens of sweat were of the so-called profuse physiologic type.

3 normal women (table 3) who could also deliver profuse palmar sweat. Samples of sweat and blood and specimens of urine were collected simultaneously, as in a glucose tolerance test. The peak values for glucose in the blood varied between 214 and 252 mg. per hundred cubic centimeters. G. N. had a peak value of glucose in the sweat of 4 mg. and D. M. a peak value of 18 mg. per hundred cubic centimeters. Both of these subjects were known to have higher than our average level for reducing substances in the sweat when fasting (table 1). The sweat glands of the other 4 subjects maintained an absolute barrier against glucose, and all samples of sweat collected from them were negative for reducing substances. The specimens of urine reduced

TABLE 3.—*Reducing Substances in Blood, Sweat and Urine Before and After the Intravenous Administration of Glucose*

Subject	Age, Years	Sex	Time After Intravenous Injection of Glucose, Minutes	Reducing Substances (Glucose), Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
				Blood	Palmar Sweat*	
G. S.	27	M	..	Fasting Values 95	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			5	214	0	..
			16	180	0	++
			30	132	0	+
			60	107	0	—
G. N.	27	F	..	Fasting Values 103	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			3.5	252	4	..
			15	173	0	+
			35	120	0	—
			60	100	0	—
D. M.	22	F	..	Fasting Values 100	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			3	252	18	..
			15	172	8	++
			36	130	4	..
			60	100	0	+
P. C.	34	M	..	Fasting Values 95	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			5	252	0	..
			10	...	..	+++
			15	173	0	..
			35	120	0	+
			60	83	0	—
R. M.	28	M	..	Fasting Values 115	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			5	235	0	..
			9	...	..	+++
			17	158	0	..
			25	..	..	+++
			35	93	0	..
			60	100	0	+
R. C.	25	F	..	Fasting Values 95	0	—
				After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)		
			5	238	0	..
			10	...	..	++++
			25	152	0	+
			60	90	0	—

TABLE 3.—*Reducing Substances in Blood, Sweat and Urine Before and After the Intravenous Administration of Glucose—Continued*

Subject	Age, Years	Sex	Time After Intravenous Injection of Glucose, Minutes	Reducing Substances (Glucose), Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
				Blood	Palmar Sweat*	
			Fasting Values			
H. F.†	18	F	..	74	0	—
			After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)			
			5	235	0	..
			20	195	0	++++
			45	139	0	..
			70	100	0	—
			Fasting Values			
R. F.†	54	F	..	100	4	—
			After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)			
			5	281	4	..
			15	...	..	+++

* All specimens of sweat were of the so-called profuse physiologic type.
† Patients who had dyshidrotic dermatitis of the hands.

Benedict's qualitative solution to reactions of 1 to 4 plus (equivalent to 500 to 3,000 mg. of glucose per hundred cubic centimeters) when the levels of blood sugar were at their peaks.

When profuse palmar sweat was studied similarly (table 3, H. F. and R. F.) from 2 subjects suffering from so-called dyshidrotic dermatitis of the hands, the results were similar.

TABLE 4.—*Fasting Levels of Reducing Substances (Glucose) in Blood, Palmar Sweat and Urine of Patients Who Had Prolonged Uncontrolled Diabetes Mellitus*

Subject	Age, Years	Sex	Physiologic Type of Sweating	Reducing Substances, Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
				Blood	Palmar Sweat	
A. K.	49	F	Profuse	210	0.0	++
R. R.	53	M	Profuse	226	0.0	+ (2.16 per cent glucose)

All these studies were made under acute conditions, and the question remained whether similar results would be obtained if the blood sugar were elevated continuously over a prolonged period. We therefore collected palmar sweat from 2 subjects who had uncontrolled diabetes mellitus. At the time of our studies, their disease had never been previously treated with diet or insulin and the levels of glucose in the blood in both subjects were more than 200 mg. per hundred cubic centimeters. The samples of their palmar sweat did not contain glucose (table 4).

SUMMARY

Forty-seven specimens of palmar sweat, collected for the study of reducing substances, were grouped into two physiologic types: (1) profuse and (2) intermittent. In seven instances both physiologic types of palmar sweat were obtained on request within a half-hour period from the same subject. There was no significant difference in the concentration of reducing substances in the two types.

The sugar barrier in the sweat gland was efficient for the most part in normal subjects with normal values for blood sugar as well as with raised levels for blood sugar. Studies on 2 subjects who had dermatitis of the hands gave similar results. Studies on 2 subjects who had uncontrolled untreated diabetes mellitus and whose levels for blood sugar had been elevated for a prolonged period also failed to show any spilling of glucose into the palmar sweat.

There was no relation between the concentration of reducing substances in the sweat and the values for glucose in blood or urine. The majority of analyses of palmar sweat revealed no reducing substances present when the values for blood sugar were normal or elevated.

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CHEMISTRY OF PALMAR SWEAT

IV. Urea

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AS PREVIOUSLY stated,[1] studies on the chemistry of palmar sweat, collected from normally functioning individual sweat glands, were undertaken with the hope that the information so gained would eventually lead to a better understanding of the "abnormal" sweat gland.

As previously reported,[1a] the chamber specially designed for these studies made it possible not only to collect pure uncontaminated sweat directly from the openings of the sweat ducts but also to observe the rate and manner of secretion of sweat from the individual ducts during the collection. Such observations [1b] have made it possible to classify into physiologic types the manner in which palmar sweat is secreted: profuse, intermittent and a combination of these two types. These studies on palmar sweat showed that the concentration of chloride is low and equal to that of thermal-regulating body sweat when the gland secretes profusely, but when it functions intermittently the palmar sweat gland can concentrate chloride as efficiently as the excreting units of the kidney.

The content of urea in general body, or thermal-regulating, sweat in both health and disease has been studied for various reasons by many observers.[2] The previously reported concentrations of urea in this

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From the Section on Dermatology and Syphilology, (Dr. Lobitz), and the Division of Clinical Biochemistry (Dr. Osterberg), Mayo Clinic.

1. Lobitz, W. C., Jr., and Osterberg, A. E.: (*a*) The Chemistry of Palmar Sweat: Preliminary Report; Apparatus and Technics, J. Invest. Dermat. **6**:63-73 (Feb.) 1945; (*b*) Chemistry of Palmer Sweat: II. Chloride, Arch. Dermat. & Syph. **56**:462-467 (Oct.) 1947.

2. Plaggemeyer, H. W., and Marshall, E. K., Jr.: A Comparison of the Excretory Power of the Skin with That of the Kidney Through a Study of Human Sweat, Arch. Int. Med. **13**:159-168 (Jan.) 1914. Barney, R. E.: Chemical Analysis of Sweat: A Preliminary Study, J. A. M. A. **85**:1373-1375 (Oct. 31) 1925. Talbert, G. A.; Finkle, J. R., and Katsuki, S. S.: Simultaneous Study of the Constituents of the Sweat, Urine and Blood, Also Gastric Acidity and Other Manifestations Resulting from Sweating: III. Urea, Am. J. Physiol. **82**:153-156 (Sept.)

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profuse dilute sweat vary between the extremes of 23.5 mg. and 400 mg. per hundred cubic centimeters of sweat (11 to 186 mg. of urea nitrogen per hundred cubic centimeters of sweat). The average range, however, is between 64 and 128 mg. of urea per hundred cubic centimeters (30 to 60 mg. of urea nitrogen per hundred cubic centimeters). All observers who studied the concentration of urea in the blood simultaneously with that in the sweat agreed that the sweat glands are capable of concentrating urea above the level of urea in the blood. Whether this is a result of the concentrating ability of an excreting unit or whether it is a property of a selective secreting unit is yet to be determined.

In our studies on the urea content of palmar sweat, the analytic method of Walker and Hudson was used.[3] In this procedure volumes of sweat even smaller than those necessary for determination of chloride could be used. In addition, by this time we had learned many methods of stimulating palmar sweating. Even more important, the persons repeatedly used as experimental subjects in these studies had also learned many ways to stimulate palmar sweating at a given time. For these reasons, in most instances, we were able to collect two separate specimens of sweat during a half-hour period. In some cases it was possible to obtain a specific type of sweating at a specific time as desired.

At the end of the period of collection of sweat, specimens of blood and urine were obtained. The specimen of urine was that amount of urine that had accumulated in the bladder during the same half-hour period during which the specimens of sweat were collected. (The volume of urine is expressed as cubic centimeters excreted per minute.) A

1927. Usher, B.: Human Sweat as Culture Medium for Bacteria, Arch. Dermat. & Syph. **18**:276-280 (Aug.) 1928. Pemberton, R.; Cajori, F. A., and Crouter, C. Y.: A Note on the Composition of Human Sweat, Ann. Int. Med. **2**:1243-1252 (June) 1929. Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, J. Biol. Chem. **99**:781-790 (Feb.) 1933. McSwiney, B. A.: The Composition of Human Perspiration, Proc. Roy. Soc. Med. **27**:839-848 (May) 1934. Mezincesco, M. D.: Composition of Human Sweat: Reaction and Chlorine, Nitrogen, Urea and Ammonia Contents, Chem. Abstr. **32**:3801 (May 20) 1938. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: III. Sweat, Arch. Dermat. & Syph. **41**:1086-1107 (June) 1940. Williams, J. W.: The Pathological Physiology of the Kidneys (and Sweat Glands) in Infections, Urol. & Cutan. Rev. **44**:47-49 (Jan.) 1940. Mickelsen, O., and Keys, A.: The Composition of Sweat, with Special Reference to the Vitamins, J. Biol. Chem. **149**:479-490 (Aug.) 1943. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934, p. 231.

3. Walker, A. M., and Hudson, C. L.: The Rôle of the Tubule in the Excretion of Urea by the Amphibian Kidney with an Improved Technique for the Ultramicro Determination of Urea Nitrogen, Am. J. Physiol. **118**:153-166 (Jan.) 1937.

single collection of sweat was continued only as long as was necessary to obtain a volume of sweat large enough for study. (The volume of sweat is expressed as length in millimeters, in a capillary tube having a uniform inside diameter of 0.35 mm. of the sweat collected per minute from fifty sweat glands.) The subjects had fasted for four hours.

The volumes of sweat were measured by the manipulative technic of Richards, Bordley and Walker,[4] the analyses for urea in the sweat were made by the ultramicro capillary tube method of Walker and Hudson,[3] and for the analyses for urea in the blood and urine the method of Van Slyke and Cullen [5] was used. The work was carried out during the spring when thermal-regulating sweat was absent during average activity. Eight men and 11 women between the ages of 21 and 48 years were studied. From these a total of seventy-seven successful collections and analysis of sweat was obtained.

The physiologic types of palmar sweating fell into two groups. Figure 1 illustrates these two types graphically: (1) the profuse con-

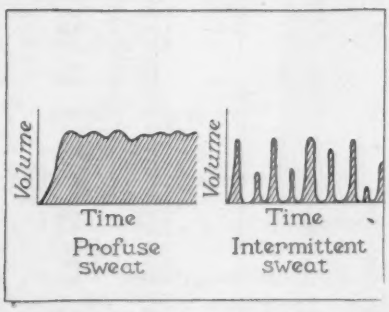

Fig. 1.—The manner of output from an individual sweat gland, the so-called profuse and intermittent physiologic types of palmar sweating.

tinuous output of sweat, (2) the intermittent output of sweat, with the sweat gland resting between bursts. We have pointed out [1b] that individual collections of palmar sweat could be compared on the basis of physiologic type even though the variability of secretion from the individual gland made it unwise to compare collections of sweat according to volume of sweat secreted (table 1).

A total of twenty-seven collections of the profuse type of sweat (fig. 2) were obtained from 3 men and 7 women. The average value for urea in the sweat was 68 mg. per hundred cubic centimeters (minimum 32 and maximum 193 mg. urea per hundred cubic centimeters of sweat).

4. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine: VII. Manipulative Technique of Capillary Tube Colorimetry, J. Biol. Chem. **101**:179-191 (June) 1933.

5. Van Slyke, D. D., and Cullen, G. E.: The Determination of Urea by the Urease Method, J. Biol. Chem. **24**:117-122 (Feb.) 1916.

TABLE 1.—*Values for Urea in Sweat, Blood and Urine*

Subject	Age, Years	Sex	Day of Month, May 1946	Physiologic Type of Sweating	Volume of Sweat, as Mm. in 0.35 Mm. I. D.* Tube per Minute, Output from 50 Glands	Volume of Urine, as Cc., per Minute, Output	Urea		
							Sweat, Mg. per 100 Cc.	Blood, Mg. per 100 Cc.	Urine, Gm. per 100 Cc.
R. C.....	24	F	7	P†	0.68	0.30	37	22	2.6
				P	0.75	....	66	..	...
			9	P	0.34	1.74	40	14	0.5
				P	0.17	....	40	..	...
			11	P	0.80	0.84	32	14	1.1
				P	0.19	....	61	..	...
A. M.....	41	F	7	I‡	0.05	0.40	130	26	2.3
				I	0.26	....	81	..	...
			9	P	0.40	1.81	40	22	0.4
				P	0.28	....	67	..	...
			11	P	0.30	0.50	59	22	1.4
				P	0.25	....	60	..	...
J. F.....	27	F	7	I	0.01	0.83	466	26	0.7
D. M.....	22	F	7	P	0.58	0.46	60	26	2.4
				P	0.12	....	67	..	...
			8	P	0.40	0.57	67	28	2.6
				P	0.35	....	59	..	...
			12	I	0.09	0.80	250	22	1.0
				I	0.06	....	250	..	...
B. M.....	48	F	8	I	0.37	1.48	112	30	1.0
			10	I	0.12	0.58	140	24	1.1
				P	0.40	....	59	..	...
			22	P	0.13	0.44	60	18	0.7
				P	0.43	....	33	..	...
D. R.....	33	M	8	I	0.04	0.64	370	24	1.4
			12	I	0.15	0.97	294	28	1.2
				I	0.13	....	213	..	...
			19	I	0.22	1.33	346	28	1.2
				P	0.37	....	176	..	...
G. N.....	27	F	9	P	0.40	0.90	47	18	1.3
				P	0.28	....	50	..	...
			11	I	0.13	4.6	75	20	0.4
				P	0.12	....	60	..	...
			14	P	0.13	1.6	60	16	0.7
				P	0.38	....	103	..	...
B. B.....	22	F	9	I	0.20	4.4	150	28	0.4
			22	I	0.03	0.4	310	24	2.6
			24	I	0.03	3.9	452	26	1.0
E. W.....	35	F	9	I	0.03	0.3	200	14	1.6
			15	I	0.09	0.7	193	16	1.0
				I	0.07	....	180	..	...
R. C.....	27	M	14	I	0.02	0.34	590	38	1.8
			16	I	0.04	0.64	620	24	1.4
E. F.....	28	M	15	I	0.12	0.89	480	34	2.2
			19	I	0.13	0.49	454	32	2.9
H. T.....	28	M	15	I	0.08	0.90	166	20	2.0
				I	0.10	....	70	..	...
J. M.....	21	F	15	I	0.07	0.26	365	28	3.1
				I	0.08	....	186	..	...
			16	I	0.08	2.65	220	18	0.5
				I	0.03	....	430	..	...
			21	I	0.014	0.38	670	20	2.0
J. B.....	29	M	17	I	0.33	0.35	120	18	1.5
				I	0.18	....	194	..	...
			19	I	0.22	1.14	160	26	0.4
				I	0.38	....	173	..	...
J. H.....	30	M	21	I	0.11	0.94	486	42	2.5
				I	0.18	....	390	..	...
			25	I	0.28	0.62	192	40	2.4
P. R.....	28	M	23	I	0.09	0.44	280	26	1.5
				P	0.90	....	98	..	...
			25	I	0.37	0.47	133	20	2.4
				I	0.10	....	230	..	...
G. P.....	32	F	10	P	0.25	0.60	53	24	1.3
				I	0.06	....	200	..	...
			12	I	0.04	0.87	120	24	1.0
				I	0.09	....	280	..	...
U. S.....	31	M	8	I	0.02	0.63	600	30	2.0
				I	0.01	....	346	..	...
			16	I	0.13	0.83	333	24	1.6
				P	0.50	....	193	..	...
E. G.....	28	F	8	I	0.07	0.71	160	28	1.6
				P	0.10	....	96	..	...
			10	I	0.33	0.55	260	28	3.0
				I	0.33	....	183	..	...
			14	I	0.14	0.50	180	34	2.4
				I	0.10	....	310	..	...

* Inside diameter. † Profuse. ‡ Intermittent.

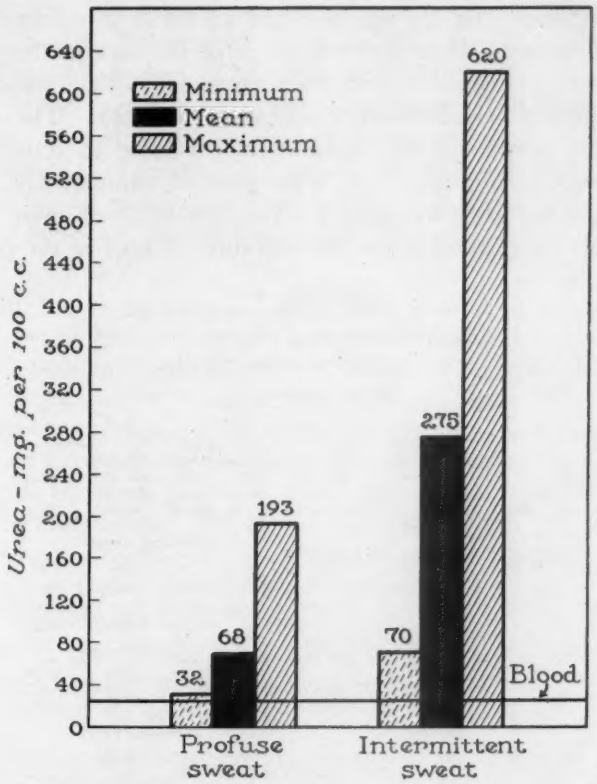

Fig. 2.—The mean values of urea (expressed as mg. urea per hundred cubic centimeters of sweat) with minimum and maximum for the two physiologic types of sweating and mean value for blood urea in all types.

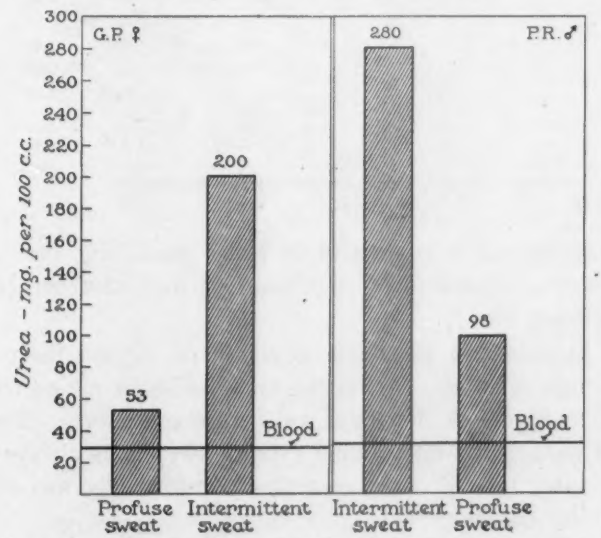

Fig. 3.—Two examples of the physiologic types of palmar sweat delivered on request in the same half-hour period by the same person. G.P. (♀) delivered her types of sweat in the reverse order from that requested from P. R. (♂).

Intermittent sweat (fig. 2) was collected a total of fifty times from 8 men and 11 women. Here the average value for urea in the sweat was 275 mg. per hundred cubic centimeters (minimum 70 and maximum 620 mg. urea per hundred cubic centimeters of sweat). The sweat gland, therefore, when working intermittently is able to concentrate urea to an extent even greater than when working continuously. The value of urea in the urine averaged 1.5 Gm. per hundred cubic centimeters and bore no relation to the concentration of urea in the palmar

TABLE 2.—*Values for Urea in Sweat, Blood and Urine Before and After Oral Administration of Urea*

Subject	Age, Years	Sex	Time After Oral Administration of Urea		Sweat Volume,* as Mm. in 0.35 Mm. I.D.† Tube per Minute per 50 Glands	Sweat Urea, Mg. per 100 Cc.	Blood Urea, Mg. per 100 Cc.	Urine		
			Hr.	Min.				Volume, Cc. per Minute, Output	Urea, Gm. per 100 Cc.	Urea, Gm. in Specimen
							Fasting Levels			
D. M.....	22	F	..	..	0.47	34	26	0.66	1.29	2.54
					0.48	51	..	....	....	....
							30 Gm. Urea (10 per Cent Solution) Orally			
			1	0	....	..	332	0.71	2.12	2.54
			1	10	0.40	277	..	....	....	....
			1	25	0.46	207	..	....	....	....
			1	40	....	..	112	2.30	3.59	3.70
			23	25	0.65	72	..	....	....	....
			23	40	0.80	75	28	0.40	3.04	0.43
							Fasting Levels			
R. C.....	24	F	..	..	0.47	36	16	0.30	1.87	0.12
					0.48	47	..	....	....	....
							16 Gm. Urea (10 per Cent Solution) Orally			
			1	0	....	..	..	0.62	3.18	1.49
			1	10	1.60	88	60	....	....	....
			1	35	1.20	77	58	....	....	....
			1	40	....	..	..	0.09	3.35	0.12
							Fasting Levels			
D. M.....	22	F	..	..	0.62	54	24	0.20	2.67	0.19
							20 Gm. Urea (10 per Cent Solution) Orally			
			0	50	....	..	..	0.33	4.08	0.73
			1	0	0.45	131	68	....	....	....
			1	30	0.45	146	78	....	....	....
			1	35	....	..	..	1.20	4.87	2.29

* All specimens of sweat were of the so-called profuse physiologic type.
† Inside diameter.

sweat. The average value for urea in the blood was 25 mg. per hundred cubic centimeters (minimum 14, maximum 42 mg. urea per hundred cubic centimeters of blood).

In seven instances we were able to collect on request the two different physiologic types of sweat in the same half-hour period from the same subject. Figure 3 illustrates two such collections. The concentration of urea in the intermittent type of sweat was always higher than in the profuse type of sweat, regardless of which type was delivered first in the thirty minute period.

To study the effect of elevated levels of urea in the blood on the palmar sweat of normal subjects we fed urea by mouth three times to persons (2 women, R. C. and D. M. [table 1]) who were known to be able to excrete profuse continuous sweat. All specimens of sweat collected were of this profuse type. Specimens of blood and urine were also collected for study. The results are shown in table 2. The level of urea in the sweat paralleled the rise and fall of urea in the blood, keeping above the level of urea in the blood at all times.

SUMMARY

Seventy-seven specimens of palmar sweat, collected for the study of urea, were grouped into two physiologic types: (1) profuse and (2) intermittent. Seven subjects were able to deliver both profuse and intermittent types of palmar sweat on request, for collection within a half-hour period. The profuse type of palmar sweat had a lower concentration of urea (mean, 68 mg. urea per hundred cubic centimeters) than the intermittent type of palmar sweat (mean, 275 mg. urea per hundred cubic centimeters). In both types, however, the concentration of urea was higher than the level of urea in the blood, but not as high as the level of urea in the urine.

On the three occasions when urea was fed by mouth to normal subjects delivering profuse palmar sweat, the level of urea in the sweat paralleled, but always exceeded, the rise and fall of urea in the blood.

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EXTENSIVE TRICHOPHYTON PURPUREUM INFECTION, WITH NEVOID ANOMALY OF THE SKIN

Report of a Case, Together with Mycologic and Physiologic Studies

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LOCALIZED dermatomycosis involving limited areas of the skin, especially of the feet, is one of the commonest cutaneous diseases. Statistics indicate that in the United States the incidence of fungous infections of the feet in large cities reaches 30 to 90 per cent of the adult population, with a higher incidence in the southern than in the northern part of the country. In spite of this high incidence, cases of more generalized dermatomycoses, affecting large areas of the skin of the trunk and of the extremities, are relatively rare. In general the widespread eruptions are caused by the same species of fungi which are responsible for the more localized forms. Unusually extensive involvement of the skin may be due to several factors, which may include either an exceptional vitality and pathogenicity of a particular strain of fungus or an abnormality of the skin itself which makes it an especially favorable substrate for propagation of the parasites. Among several species of fungi which are capable of producing generalized dermatomycoses Trichophyton purpureum occupies an important place, at least in this country.

Thus Lewis and Hopper [1] stated that T. purpureum is one of the fungi which cause lesions involving large surfaces of skin of the trunk and of the extremities, at times of a bizarre and configurate type or resembling psoriasis or even simulating tinea imbricata.

Lewis, Montgomery and Hopper [2] observed 3 instances of eruptions caused by T. purpureum and involving large areas of the skin of the trunk. One of these patients presented large circinate plaques on the

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This case was presented by the authors on May 2, 1946 before the Section of Dermatology and Syphilology of the New York Academy of Medicine.

1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943, pp. 76 and 79.

2. Lewis, G. M.; Montgomery, R. M., and Hopper, M. E.: Cutaneous Manifestations of Trichophyton Purpureum (Bang), Arch. Dermat. & Syph. **37**:823 (May) 1938.

chest, the left shoulder and the back. On the left hand and the fingers there were erythematosquamous and papular lesions. Circinate patches were also present on the left wrist. The skin of the left palm was thickened and scaly. Both soles were erythematous, thickened and scaly. Scaly patches were present on the dorsum of the foot. The authors stated that the lesions of the glabrous skin should be differentiated from atypical psoriasis, neurodermatitis and erythema annulare centrifugum. The lesions on the hands and feet may also simulate eczema, calluses and arsenical keratoses.

One of us [3] described 2 cases of generalized infection of the skin by T. purpureum. One patient presented erythematosquamous patches of various sizes on the abdomen, groins and lower extremities. In another patient an eruption of the same type involved large areas on the trunk and upper and lower extremities, including the palms and the soles. All finger nails and all but two toe nails were also affected.

Tolmach and Schweig [4] described a case of T. purpureum infection involving almost two thirds of the entire skin. There were large sharply marginated patches, with serpiginous bizarre contours. The unusual feature of this case was the presence of vesicular and papulovesicular lesions, which suggested dermatitis herpetiformis. This clinical diagnosis had been made by a number of competent dermatologists before the mycologic studies established the fungous causation of the disease.

Lewis [5] presented a patient with lesions on the feet, various parts of the body, scalp and beard. T. purpureum was cultured from several areas, including the scalp and beard.

Ayres [6] presented a patient with erythematous scaly lesions on the face, ears, feet, ankles and buttocks. A number of toe nails were also affected. T. purpureum was cultured from several areas. This patient also had lesions on the mucous membrane of the mouth, from which Monilia albicans was recoverable in cultures.

There are two reports which are of particular interest in connection with the case described in the present communication: Lane [7] presented a patient who had generalized ichthyosis since birth and whose fungous eruption on the chest, back, buttocks and thighs consisted of foci with

3. Muskatblit, E.: Observations on Epidermophyton Rubrum or Trichophyton Purpureum, Mycologia **25**:109 (March-April) 1933.

4. Tolmach, J. A., and Schweig, J.: Generalized Trichophyton Purpureum Infection Simulating Dermatitis Herpetiformis, Arch. Dermat. & Syph. **41**:732 (April) 1940.

5. Lewis, G. M.: Dermatophytosis, Tinea Barbae and Tinea Corporis Due to Trichophyton Purpureum, Arch. Dermat. & Syph. **41**:938 (May) 1940.

6. Ayres, S., Jr.: Dermatophytosis Due to Trichophyton Purpureum with Monilia Infection of the Mouth, Arch. Dermat. & Syph. **51**:285 (April) 1945.

7. Lane, C. G.: Tinea Corporis (Trichophyton Purpureum); Moniliasis of Feet; Ichthyosis, Arch. Dermat. & Syph. **40**:119 (July) 1939.

red raised borders, forming geometric and polycyclic patches. Cultures of material from the body showed T. purpureum. The interdigital webs of the feet were macerated, and M. albicans was cultured from there. Swartz and Conant [8] observed 4 cases of extensive lichenified eruption caused by T. purpureum. One of the patients, who also had ichthyosis, had papular lichenified lesions on the upper and lower extremities, the lower part of the trunk, the chest and the suprapubic area. The toe nails of the right foot were also affected and were discolored and deformed. The other patients presented circular and gyrate lesions, with lichenified papular borders and also lichenified plaques of various sizes over the legs, arms and trunk.

REPORT OF A CASE

A. R., a white man aged 24, when first seen on June 19, 1945 in the private practice of Dr. Marion B. Sulzberger and one of us (R.L.B.), stated that he had an eruption on both palms and soles since birth and an eruption on the body and other parts of the extremities since the age of 13 or 14.

The patient's parents were not related; his only sister had no cutaneous abnormalities, and there was no other family history of cutaneous diseases.

In 1937 the patient was hospitalized at the Beth Israel Hospital in Boston, and the diagnosis of acanthosis nigricans was made. There were dryness and cracking of the nails in addition to an eruption on the feet, hands, abdomen, thighs and back. No examination for fungi was carried out at that time.

In December 1943 the patient was seen at the New York Skin and Cancer Unit, where a clinical and histologic (biopsy specimen was taken from the back) diagnosis of erythroderma ichthyosiforme congenitum was made. The patient was presented [9] at the New York Academy of Medicine under this diagnosis, which was accepted by those present.

When first seen by us in June 1945, A. R. presented the following cutaneous changes: There was an extensive generalized somewhat erythroderma-like eruption, covering the hands (fig. 1), forearms, arms, feet, legs, thighs, neck, chest, back and abdomen (fig. 2). The lesions on the arms and legs consisted of large gyrate and circinate slightly scaly areas which were brownish, infiltrated and lichenified, with well defined and raised borders. These lesions somewhat resembled a relief map, and the intervening skin appeared normal. The patient stated that the shapes of these lesions changed gradually in that previously unaffected areas became affected and vice versa.

The neck presented well defined, but only slightly elevated, erythematous and scaly circinate patches. The trunk was the site of diffuse scaling, dryness, thickening and yellowish brown to brownish red discoloration in large areas. Some of the borders of these large areas were also well defined.

On the palms and soles there was decided hyperkeratosis, with some heaping and fissuring of horny material. All the finger nails and toe nails were yellowish, brittle, fissured and misshapen. The nails had been filed down by the patient, as

8. Swartz, J. H., and Conant, N. F.: Extensive Lichenified Eruption Caused by Trichophyton Rubrum, Arch. Dermat. & Syph. **42**:614 (Oct.) 1940.

9. Rosen, I.: Erythroderma Ichthyosiforme Congenitale, Arch. Dermat. & Syph. **51**:161 (Feb.) 1945.

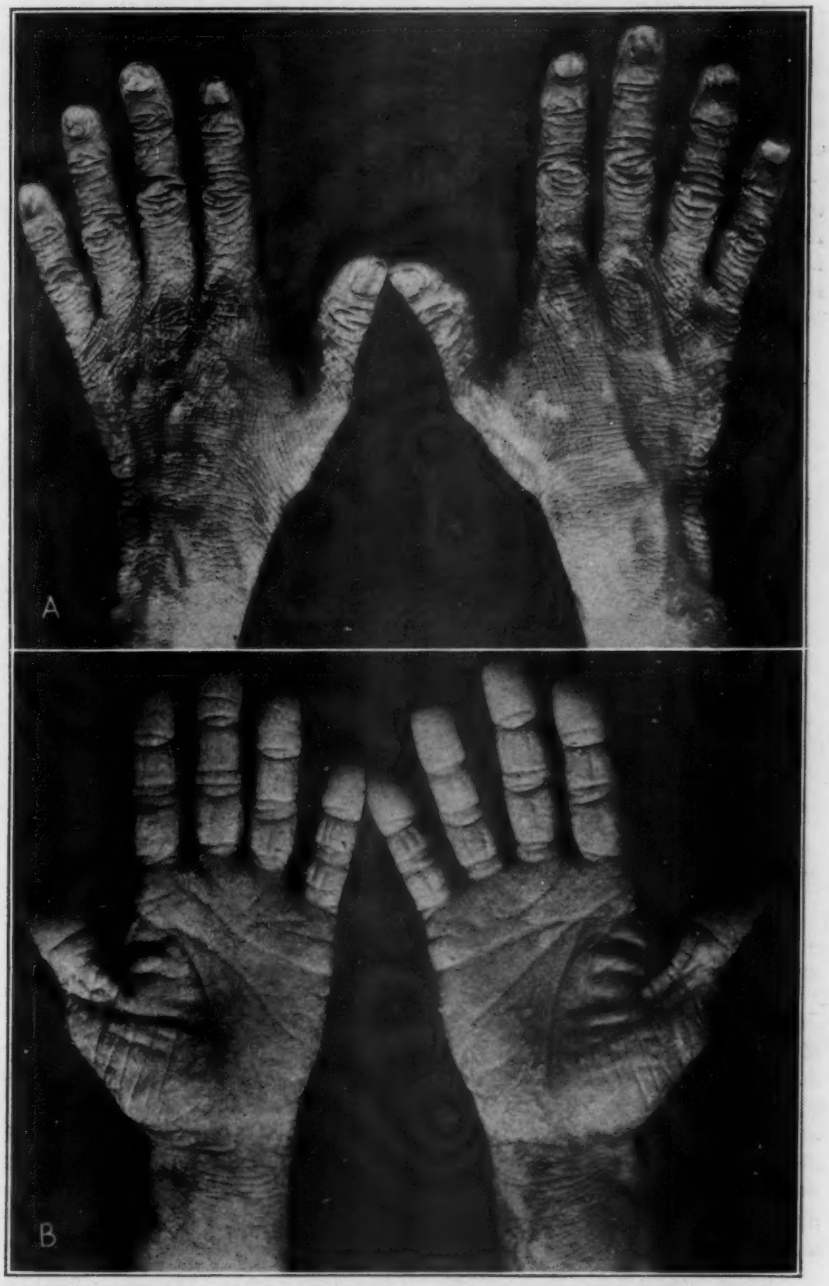

Fig. 1.—*A*, dorsa of the hands, showing thickening, lichenification and scaling. The nails are almost spoon shaped because of their having been filed down by the patient. *B*, palms, showing hyperkeratosis and scaling. On the right wrist fairly well defined borders of scaly hyperpigmented patches are seen.

failure to do so always resulted in a heaped-up nail which interfered with his activities.

Because of the well defined borders of parts of the eruption and the presence of circinate patches, scrapings from different areas of the body were taken for microscopic and cultural examination for fungi. Characteristic fungous mycelia were microscopically seen in specimens from the chest, shoulder, arm, neck and center of the back.

On Sabouraud's dextrose peptone agar the culture obtained from the scrapings from the neck was white, downy and hemispheric in shape. It grew side by side with saprophytes, and in order to save the strain for further study three transfers into a fresh tube were made. The three colonies which developed after six weeks of growth were of different configuration (fig. 3). The uppermost culture, growing on a thin layer of the medium, had a heaped-up center sur-

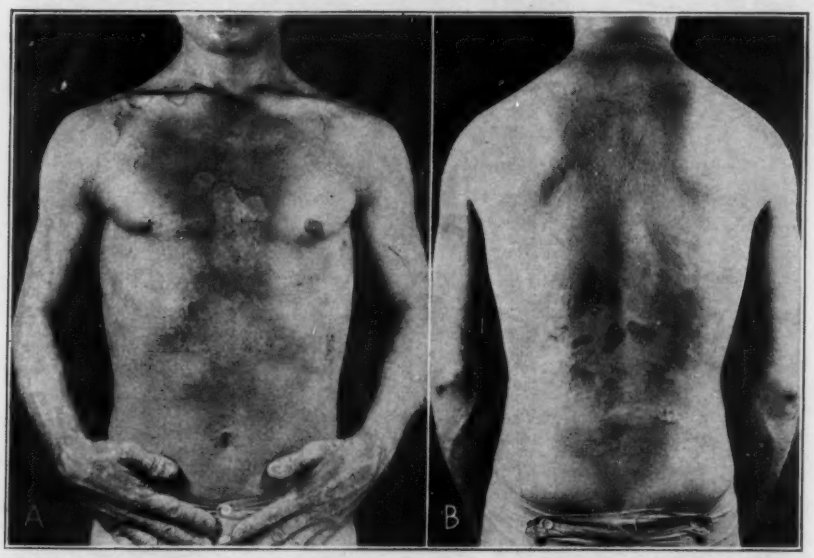

Fig. 2.—*A*, severe generalized involvement of the front of the body, with circinate, gyrate and polycyclic lesions. *B*, diffuse erythema and scaling over the upper part of the back and buttocks; circinate and gyrate lesions of the middle and lower parts of the back.

rounded by a wide flat zone. The middle colony showed a well formed crater in the center, with a depression and an elevated wall around it. The colony at the bottom of the tube, growing on a heavier layer of the medium, was cerebriform, with numerous grooves and rounded convolutions. The surface was velvety and like a fine powder. The color was white with a faint rose tinge. The back surface showed red pigmentation, especially noticeable under the edge of the colony near the wall of the tube. A single point transfer into a fresh tube developed the same morphologic picture.

Culture mounts made in lactose phenol blue (fig. 4 and 5) revealed a mass of septate and branched hyphae, a moderate number of small spores (microconidia) and a great number of macroconidia. The latter were of a tapering type, long,

finger-like, more cylindric than fusiform, with thin and smooth walls and numerous cross walls dividing them into several compartments. This species was identified as T. purpureum.

The patient was seen again December 14, when seven separate specimens of scrapings were taken from different lesions, namely, the wrists, palms, thighs, toes, soles, finger nails and toe nails. All the specimens which were examined microscopically in potassium hydroxide showed the presence of fungi in the form of long septate and branched filaments (fig. 6). Material from the same seven specimens of scrapings were planted on Sabouraud's medium, three tubes for each specimen. In spite of the large amount of material used, it proved impossible to

Fig. 3.—Cultures from the neck on Sabouraud's dextrose peptone agar, showing T. purpureum. Left, six weeks old and right, three weeks old.

isolate the pathogenic fungus because of an abundant growth of various saprophytes in all tubes.

After the diagnosis of generalized dermatomycosis due to T. purpureum had been made, the patient was given various forms of local treatment, none of which was used more than once or twice because the patient objected to the physical properties or the odor of the preparations.

On Jan. 21, 1946 the patient was given an oil in water emulsion cream[10] which contained coal tar, sulfur and salicylic acid.

10. "Pragmatar" (Smith, Kline & French Laboratories).

After an absence of almost three months he was again seen on April 11. The eruption on his body had cleared with the following exceptions: There was still thickening of the dorsa of the fingers and to a slight degree of the dorsa of the

Fig. 4.—Culture mount of T. purpureum in lactose phenol blue, showing mycelium with microconidia. × approximately 479.

metacarpal area and the wrists. The finger nails were dry, brittle, slightly yellowish and fissured; they had been shaved down with a razor blade. On the palms there was hyperkeratosis extending to the wrists. On the legs there were lichenified, thickened, brownish, slightly scaly and hyperkeratotic well defined

patches, of various shapes and sizes. There was hyperkeratosis of the heels. The soles were greatly hyperkeratotic and thickened, with formation of deep clefts in the hyperkeratotic areas. The toe nails were yellowish and onychogrypotic. Microscopic examination of scrapings taken on May 10 from the palms and fingers,

Fig. 5.—Culture mount of T. purpureum in lactose phenol blue, showing multiseptate macroconidia. × approximately 468.

two finger nails, the right sole and one toe nail showed again fungous mycelia. No mycelia were found in material from one of the hyperkeratotic patches on the

legs. On Sabouraud's medium cultures of material from the same areas failed to show any growth of pathogenic fungi.

Dr. Wilbert Sachs, of the New York Skin and Cancer Unit, reviewed the sections of the biopsy specimen taken from the back in 1944 and reported an

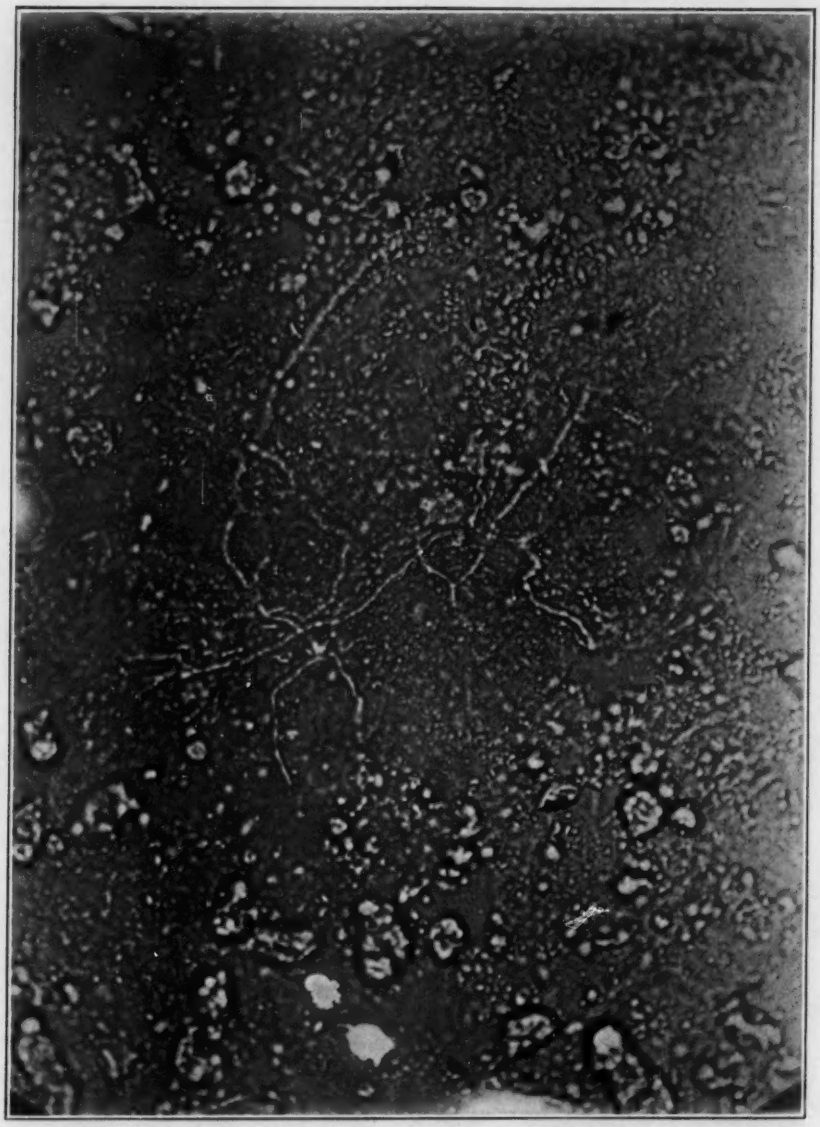

Fig. 6.—Fungi in scrapings from the finger nails (potassium hydroxide preparation). × approximately 492.

ichthyosiform type of process on the basis of the following observations: The epidermis was irregularly acanthotic. The surface was verrucous and covered

with a densely laminated horny layer. The granular layer was present throughout. The palisade layer was intact, and no important changes were seen within the epidermis. The vessels of the upper layer of the cutis were dilated, and about them was a pronounced reaction involving small round cells, wandering connective tissue and plasma cells. There was a similar reaction about all sweat ducts. No mycelia were seen in the horny layer. There was a moderate amount of interstitial edema in the cutis.

Sweat Production.—When first seen A. R. stated that he did not perspire at all except on the neck, face and scalp. For years he had often felt "extremely hot" because of his inability to sweat on the body. As he is a saxophone player who frequently has to work in overheated rooms, the inability to perspire caused a great deal of discomfort during all seasons of the year. When A. R. was seen again in April 1946, after the rash on his body had cleared, he remarked that for the first time he was perspiring on the body.

Studies on the quantitative output of water through the sweat of A. R. were carried out on May 9 by Dr. Franz Herrmann of the New York Skin and Cancer Unit. These studies, in which a fluorescence method was used,[11] showed that, except on the face, A. R. had an abnormally low production of sweat, i.e., almost a complete absence of sweat when he was at rest with "normal" room temperature. However, after insertion of one arm into a heating device at 85 C. (185 F.) for thirty minutes, there was, in general, only slightly less sweating on the body than in normal persons.

P_H of the Skin.—On Dec. 13, 1945, while A. R. still had his generalized eruption, determinations of the p_H were made on twenty-two affected and unaffected areas of the skin. The method of Bernstein and Herrmann[12] was used. The values for the p_H of the face and retroauricular areas were 4.2, 4.3 and 4.5, while the values on the rest of the body were between 4.3 and 6.5, with an average value of 5.5. No significant differences were found between affected and unaffected cutaneous areas on the body.

Twelve additional determinations of p_H were done by Dr. Franz Herrmann on May 9, 1946, at a time when the eruption on the patient's body had cleared except for the areas aforementioned. The p_H on the forehead was 4.9. The values on the rest of the body were between 3.7 and 5.6, with an average value of 4.3.

COMMENT

This case of generalized dermatomycosis is of interest not only because of its unusual extent but because of the cutaneous changes which probably preceded and which were associated with the fungous infection. It appears probable that the diagnosis of erythroderma ichthyosiforme congenitum which had been made in 1944 [9] was incorrect. However, there is little doubt that this patient had a nevoid anomaly of the skin. The evidence in favor of such an anomaly can be summarized as follows: (1) the presence of palmar and plantar hyperkeratosis since birth, (2) decided changes in the finger nails and toe nails, including definite onychogryposis of the toe nails (could have been due to fungous infec-

11. Hand, W. C.: Personal communication to the authors.

12. Bernstein, E. T., and Herrmann, F.: The Acidity on the Surface of the Skin, New York State J. Med. **42**:436 (March 1) 1942.

tion), (3) the presence on the legs of a few patches which, as far as could be ascertained, were free from fungous infection, and the appearance and persistence of which suggested a nevoid character, (4) nevoid changes in skin from the back on histologic examination in 1944, (5) the absence of sweating on the body and the symptoms of anhidrosis, as described by the patient, up to the time of clearing of the body eruption in 1946 (could have been due to fungous infection) and (6) the abnormally low output of sweat on the body at normal temperatures when the patient was at rest and the somewhat low output of sweat on the body with deliberate stimulation of sweating through exposure to heat, as was demonstrated in laboratory tests after the eruption on the body had cleared.

The previously reported cases of generalized T. purpureum infections in patients with ichthyosis [13] and the findings in our patient A. R. suggest that the susceptibility to fungous infection and the severe generalization and persistence of the infection may in these patients have been due to the underlying nevoid anomaly of the skin. In our patient this congenital anomaly probably furnished an excess of horny tissue and thus a fertile soil for the growth of the fungi and may have led to a lack of fungicidal substances, in particular fatty acids,[14] because of the relative or complete absence of sweat on the body. The theory that all the changes in this patient were caused by a fungous infection during early childhood has been suggested,[15] but only as a remote and unlikely possibility.

We should like to call particular attention to the relative ease with which the fungous infection on the body cleared under treatment, once a remedy had been found that the patient was willing to use. This point is of particular interest in connection with the recent discussions on the relative resistance and lack of resistance, respectively, to treatment of fungous infection due to T. purpureum.[16] Another point of interest is the fall in the p_H of the skin of the body subsequent to the clearing of the eruption on the body and the clinically noticeable appearance of sweat on the body. The average p_H of the body fell from 5.5 to 4.3, while there was no significant change in the p_H of the face, which apparently had always had a quantitatively normal secretion of sweat.

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13. Lane.[7] Swartz and Conant.[8]

14. Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, J. Invest. Dermat. **1**:237 (Aug.) 1938; correction, ibid. **1**:398a (Oct.) 1938.

15. Sulzberger, M. B.: Personal communication to the authors.

16. Lewis and Hopper.[1] Weidman, F. D., and Glass, F. A.: Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet: A Comparison of Therapeutic Methods, Arch. Dermat. & Syph. **53**:213 (March) 1946.

SUMMARY

A case is reported of a nevoid anomaly of the skin, associated with a generalized and unusually extensive fungous infection due to T. purpureum. It is suggested that the nevoid anomaly of the skin, leading to an excess of horny tissue (including keratosis palmaris et plantaris) and to a relative lack of sweat, may have been a factor in making this patient's skin unusually susceptible to the fungous infection. It is pointed out that such factors may be operable in other severe, extensive or otherwise unusual fungous infections. The ready response to simple external treatment supports the concept that T. purpureum infections are not necessarily always refractory to local treatment.

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KAPOSI'S VARICELLIFORM ERUPTION

Isolation of the Virus of Herpes Simplex from the Cutaneous Lesions of Three Adults and One Infant

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AND

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CINCINNATI

TOWARD the end of the last century Kaposi [1] described a syndrome in children. The young patients experienced an eruption and a febrile reaction as a complication of preexisting atopic dermatitis. Lesions usually appeared over the old atopic dermatitis, but occasionally invaded the neighboring healthy skin. The lesions went through various stages of vesiculation, umbilication, desiccation and rupture. The acute lesions appeared in recurrent crops for many days, and when they finally healed only signs of the original atopic dermatitis persisted. No mention was made in the original description of lymph node involvement, which was a common observation in subsequent reports of similiar cases. Shortly thereafter, under the title of "Pustulosis acuta varioliformis," Juliusberg [2] described a fatal case in which there were lesions similar to those of Kaposi's varicelliform eruption. A similar disease picture has been described by many authors under the name of eczema vaccinatum. Many of these persons had been exposed to a recently vaccinated member of the family or had themselves been recently vaccinated. Vaccine virus was recovered [3] or Guarnieri bodies were demonstrated [4] from the cutaneous lesions of several patients with an eruption

From the Children's Hospital Research Foundation and the Departments of Pediatrics, Bacteriology and Dermatology and Syphilology of the University of Cincinnati College of Medicine.

1. Kaposi, M.: Pathology and Treatment of Diseases of the Skin, New York, William Wood & Company, 1895, p. 346.

2. Juliusberg, F.: Ueber Pustulosis acuta varioliformis, Arch. f. Dermat. u. Syph. **46**:21, 1898.

3. Hershey, F. B., and Smith, W. E.: Generalized Vaccinia in an Eczematous Child, Am. J. Dis. Child. **69**:33 (Jan.) 1945.

4. Freund, H.: Zur Aetiologie der pustulosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52 (Jan.) 1934. Ellis, F. A.: Eczema Vaccinatum: Its Relation to Generalized Vaccinia; Report of Two Cases, J.A.M.A. **104**:1891 (May 25) 1935. Pepple, A. W.; Murrell, T. W., and Fowlkes, R. W.: The Varicelliform Eruption of Kaposi, South. M. J. **35**:667 (July) 1942.

resembling that described by Kaposi. Recently the virus of herpes simplex has been isolated from several patients presenting the syndrome,[5] and it is now thought that there are at least two similar eruptions which occur on eczematous lesions—one caused by the virus of vaccinia and known as eczema vaccinatum and the other caused by the virus of herpes simplex and known as Kaposi's varicelliform eruption.

Of 96 cases of Kaposi's varicelliform eruption recorded in the literature 75 occurred in children and only 21 in adults. Of the patients whose exact age was recorded, 24 or 32 per cent were infants in the first year of life. The death rate was 23 per cent in infants and 9 per cent in adults. It seems probable that this is a higher death rate than actually obtains, as many milder cases probably were not recorded.

The following report is of 4 cases of Kaposi's varicelliform eruption, all of which were seen within a short period of time. The fact that 3 of the patients were adults appears of importance, as the disease is apparently much less common in adults than in children and the causative agent has been isolated from the lesions of adults only twice.[6] All 4 patients gave a history of definite exposure to the virus of herpes simplex. Strains of herpes simplex were isolated from the cutaneous lesions of all.

REPORT OF CASES

CASE 1.—J. M., a 14 month old white boy, was admitted to The Children's Hospital Nov. 26, 1945, because of infected atopic dermatitis. The patient had had atopic dermatitis since 1 month of age and had been admitted to the hospital with the same complaint in April 1945. There was a familial history of atopy. The child had not been vaccinated, nor was there any history of recent exposure to vaccine virus. However, the mother had had "fever blisters" less than a week before the child's admission. The child's temperature on admission was 103.4 F. He was acutely ill and irritable. The skin of the face and neck was red and scaling, and over a large area of the face the lesions were secondarily infected and crusted. There were large fluctuant lymph nodes behind the right ear. Chronic eczematoid lesions appeared around the hands, popliteal and cubital spaces. The trunk was relatively free of lesions, but the skin was dry, scaly and excoriated. The tonsils were enlarged and the pharynx injected. There was slight edema of the feet. The patient was given penicillin intramuscularly. Two days after admission a post-

5. (*a*) Wenner, H. A.: Complications of Infantile Eczema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**:247 (April) 1944. (*b*) Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption: Review of the Literature and Report of Two Cases of Its Occurrence in Adults, Arch. Dermat. & Syph. **50**:99 (Aug.) 1944. (*c*) Blattner, R. J.; Heys, F. M., and Harrison, M. L. K.: Etiology of Kaposi's Varicelliform Eruption, J. Pediat. **27**:207 (Sept.) 1945. (*d*) Lynch, F. W.; Evans, C. A.; Bolin, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption: Extensive Herpes Simplex as a Complication of Eczema, Arch. Dermat. & Syph. **51**:129 (Feb.) 1945. (*e*) Jaquette, W. A.; Convey, J. H., and Pillsbury, D. M.: Kaposi's Varicelliform Eruption: Studies on Etiology, Am. J. Dis. Child. **71**:45 (Jan.) 1946.

6. Barton and Brunsting.[5b] Lynch, Evans, Bolin and Steves.[5d]

auricular abscess on the right side was drained. At the same time a varicelliform eruption developed on the face and nose, with some scattered lesions over the rest of the body. The lesions were discrete, umbilicated and superimposed on the eczematized area. Herpetic lesions were noted on the inner surface of the lips and gums. A diagnosis of Kaposi's varicelliform eruption was made.[7] The temperature rose to 105.0 F. and remained elevated until December 3, when it dropped to normal and then rose to 102.5 F. on December 7 and remained above 100 F. until December 11, at which time penicillin therapy was discontinued. A transfusion of 150 cc.

Fig. 1.—Kaposi's varicelliform eruption (case 1).

of whole blood was given. The temperature remained elevated, and on December 13 it rose again to 102.0 F. Penicillin was given for four more days, and penicillin ointment was used on the skin. Sulfadiazine was also used. Because it was thought that the fever might be due to the extensive involvement of the skin, with interference with the sweating mechanism, the patient was placed in a cool quiet room. The temperature dropped dramatically to normal and remained normal until the time of discharge on the thirty-eighth day of hospitalization. At this time the herpetic lesions were almost entirely healed, but the atopic dermatitis remained. Culture of the auricular abscess on November 28 revealed a pure culture of hemolytic streptococcus. The blood culture was sterile on December 2. The urine was

7. Diagnosis was made by Dr. Leon A. Goldman of the Department of Dermatology and Syphilology.

essentially normal. Leukocyte counts ranged between 9,800 and 11,200. The differential counts were not remarkable. The hemoglobin varied from 8.7 to 13.6 Gm. and the erythrocytes from 3,600,000 to 4,500,000. The albumin-globulin ratio was 3.4 to 3.0. Crusts and vesicular exudate obtained from lesions on the face on November 29 were applied to the scarified corneas of a rabbit. Keratoconjunctivitis developed in both eyes.

CASE 2.—F. R., a white boy aged 16, had had atopic dermatitis of varying severity since infancy. For three or four months previous to the present episode the face, ears, neck and cubital spaces had presented only a dry scaling eczematoid eruption. Four days previous to admission to Christ Hospital he experienced acute dermatitis superimposed on all the eczematized areas. On examination numerous lentil-sized umbilicated vesicles and pustules surrounded by red halos were seen. These were closely set over the face and neck and grouped on the arms and chest, with discrete lesions scattered over the trunk. The lesions on the face and neck were pustular, had in large part become confluent and were in many areas ruptured. These areas were oozing and crusted. There was edema of the eyelids, face and neck. There was decided cervical lymphadenopathy. The temperature on admission was 102.0 F. The leukocytes numbered 16,000, erythrocytes 4,540,000, polymorphonuclear leukocytes 93 per cent, small lymphocytes 4 per cent and mononuclear cells 3 per cent. The hemoglobin measured 13.5 Gm. Cultures of the urine and blood were sterile. A culture of the lesions revealed Bacillus coli, hemolytic Staphylococcus albus and an unidentified gram-negative coccus. An agent capable of provoking keratoconjunctivitis in rabbits was obtained from the early cutaneous lesions. The patient's temperature rose rapidly to 105.0 F. He became irrational and at intervals drowsy. Penicillin was administered parenterally and topically, without apparent effect. He was given 1 unit of pooled plasma on two occasions forty-eight hours apart, with no apparent benefit. Two intravenous infusions of 1,000 cc. of 5 per cent solution of dextrose in isotonic solution of sodium chloride with 10 grains (0.65 Gm.) of acetylsalicylic acid apparently reduced the temperature, and temporary general improvement followed. After five days the isolated lesions became crusted, new lesions ceased forming, the swelling decreased and the temperature dropped. Recovery was steady from this point on. The acute cutaneous lesions healed in fourteen days, leaving tiny atrophic areas. The atopic dermatitis was unchanged. The patient had been successfully vaccinated at the age of 2 years and had no known exposure to a recently vaccinated person. Eight and ten days before his acute infection he had been exposed to his older brother and father, both of whom had labial herpes. The patient himself had not experienced previous herpetic infection.

CASE 3.—E. B., a white woman aged 25, had had atopic dermatitis since childhood. At the time of onset of the present eruption she presented only a dry slightly scaling eczematoid eruption on the face, neck and cubital areas. On Feb. 11, 1946 she experienced burning and itching on the neck and face. A few hours later lentil-sized vesicles on an inflammatory base appeared. Swelling of the face, neck and eyelids and cervical lymphadenopathy followed. On admission to Christ Hospital on February 12 the temperature was 100.0 F. The leukocytes numbered 4,900, the erythrocytes 4,120,000, polymorphonuclear leukocytes 77 per cent, eosinophils 3 per cent, small lymphocytes 12 per cent and mononuclear cells 8 per cent. The hemoglobin measured 13 Gm. The urine was normal. An agent capable of provoking keratoconjunctivitis in rabbits was isolated from the cutaneous lesions and proved to be herpes. The patient was given 2 units of pooled plasma forty-eight hours apart, without apparent change locally or systemically. Penicillin wet dressings and, later, penicillin ointment were used topically. Thiamine and sodium

salicylate were given orally. Her temperature continued at 100.0 F. for eight days and then subsided. The lesions crusted; swelling disappeared, and the areas healed leaving a few tiny pits. The underlying atopic dermatitis showed little change from its status before the acute episode. The patient had been successfully vaccinated when a child, and a subsequent vaccination, in her "teens," had failed to take. She had for six days been exposed to her fiance, who had labial herpes. The eruption appeared five days after the last exposure. The patient was sure that she had not previously had herpetic infection.

Three weeks after the onset of the acute eruption typical labial herpes developed, one lesion on the upper and one on the lower lip. The lesions ran the usual course of labial herpes and disappeared in a few days. Seventeen days later red papules appeared on her forehead and in forty-eight hours spread over the whole face. Three days after the onset of the eruption the lesions were vesicular, lentil sized and umbilicated. Some of the lesions in this attack were small vesicopapules and did not form vesicles. The whole surface of the face and neck was erythematous. Discrete lesions on the chest and back, outside the confluent areas, had decided erythematous halos. The patient was again hospitalized. Her temperature was 101.2 F. The leukocytes numbered 5,750 and erythrocytes 5,000,000. The hemoglobin measured 14.5 Gm. The urine was clear. Penicillin wet dressings were applied locally. Thiamine and sodium salicylate were administered orally. One unit of pooled plasma was given intravenously, without apparent effect. On March 28 the leukocytes numbered 4,200 and on March 31, 5,000. She again experienced edema of the neck and cervical lymphadenopathy. After five days her temperature became normal and her herpetiform lesions cleared, leaving her atopic dermatitis somewhat reddened. She was discharged from the hospital on April 1. The atopic dermatitis subsided within a few days with soothing topical measures. Inoculation of material from the acute cutaneous lesions on a rabbit's cornea was inconclusive as to the presence of herpes virus.

Case 4.—H. T., a white woman aged 23, had atopic dermatitis from 4 to 12 months of age. It recurred at 5 years of age, cleared in one and one-half years and recurred again for a period of two years at 13 years of age. She was first seen in July 1945 with atopic dermatitis, which had been present for the past year. The cutaneous involvement was generalized but was accentuated on the face, neck and flexure surfaces of the extremities. After treatment in Christ Hospital for two months the atopic dermatitis was brought under reasonable control. Subsequently, the course of the disease until the patient was readmitted to the hospital, April 25, 1946, was fluctuating. Periods of moderate exacerbation of the eruption alternated with periods during which the skin was relatively clear. Forty-eight hours prior to readmission, the patient complained of feeling drowsy and tired. She noted enlargement of the lymph glands of her neck. Twenty-four hours before readmission, the entire cutaneous surface became erythematous; she experienced fever, and vesicles appeared on her face and neck. On admission she presented an eruption that was generalized except for a few clear areas on her trunk and legs. The face, neck and arms were confluently involved. The lesions were lentil sized, umbilicated vesicles. The face and neck were edematous, and serum was oozing from the cutaneous lesions. A decided cervical lymphadenopathy was present. Discrete and grouped lesions, with inflammatory halos, appeared over the other areas of the body. The temperature was 105.0 F. The leukocytes numbered 4,000, polymorphonuclear leukocytes 90 per cent, eosinophils 1 per cent, basophils 1 per cent, small lymphocytes 4 per cent and mononuclear cells 4 per cent. The urine was normal except for a faint trace of albumin. An agent capable of pro-

voking keratoconjunctivitis in rabbits was isolated from the cutaneous lesions. Penicillin was administered topically and parenterally. She received 2 ampules of immune globulin intramuscularly daily. New lesions appeared in crops for five days, and the skin of the face, neck, chest, back and arms became covered with confluent oozing denuded areas. The temperature reached levels between 105.0 and 106.0 F. daily. Blood cultures were sterile. The leukocytes fell to 3,000 on April 26 and to 2,000 on April 27. "Pentnucleotide" N.N.R. and dextrose were given intravenously. The cutaneous lesions on the legs and thighs and some of those on the arms became crusted and were healing by May 1. On this day the patient became disoriented and irrational. She died on May 2 of respiratory failure. The patient had been successfully vaccinated at the age of 7 years, and two subsequent vaccinations had been unsuccessful. She had no history of preceding herpetic infection. For about ten days before the fatal disease developed she had been exposed to her fiance, who had labial herpes.

LABORATORY DATA

In the preceding reports it was stated that an agent capable of provoking keratoconjunctivitis in rabbits was obtained from the cutaneous lesions of 4 patients with Kaposi's varicelliform eruption. This agent was identified as herpes virus through host susceptibility, histologic studies of the lesions obtained in the host, cultural studies and filtration experiments. Neutralization tests were performed with homologous and heterologous strains of the virus and the patients' serums in order to establish a relationship of the agent to the disease. Cross immunity tests in mice and rabbits were made to show the relationship to a known strain of herpes simplex.

Methods and Materials.—Animals: Animals included in the various tests were rabbits, hamsters and mice. The mice were albinos of either sex, supplied by a local dealer. Mice weighing between 10 and 18 Gm. were used for the titrations, neutralization tests and routine passages. When injections were made peripherally, in order to obtain immune survivors, mice weighing approximately 22 Gm. were employed.

Inoculums: (*a*) Vesicular fluid was obtained by puncturing relatively fresh vesicles on the patients' skin with a sterile cataract knife. A cotton swab previously moistened with sterile isotonic solution of sodium chloride was lightly wiped over the area. The material was then used to rub onto the scarified cornea of a rabbit.[8]

(*b*) The nictitating membrane or a piece of the rabbit's cornea was removed as aseptically as possible, washed with several changes of sterile isotonic solution of sodium chloride and ground with alundum in about 1 cc. of isotonic solution of sodium chloride. The suspension was centrifuged at 1,500 revolutions per minute for a few minutes, and the clear supernatant fluid was used for inoculation of mice and cultures on blood agar plates. The supernatant and sediment were then mixed again, and a swab of the crude suspension was rubbed on the scarified cornea of another rabbit.

(*c*) The brains were removed aseptically from infected moribund mice, weighed and ground in a mortar with alundum to make a 10 or 20 per cent suspension.

8. Scarification of rabbits' corneas and intracerebral inoculations were performed while animals were under full ether anesthesia.

After centrifugation the supernatant was removed. Isotonic solution of sodium chloride was the diluent used for the routine cerebral mouse passages, and rabbit serum in isotonic solution of sodium chloride[9] was used for the titrations and neutralization tests. Occasionally, for storage in solid carbon dioxide, brain suspension was prepared in undiluted rabbit serum. For the maintenance of strains entire infected mouse brains were placed into "lusteroid" tubes and stored in solid carbon dioxide. When needed the frozen brain was dropped from the "lusteroid" into a mortar, while still frozen, and then triturated as described. It was observed that all strains of virus could be maintained in solid carbon dioxide for long periods. As a rule mice received 0.03 cc. of inoculum intracerebrally and amounts ranging between 0.1 cc. and 0.5 cc. intraperitoneally. Intracerebral titrations in mice gave LD_{50} titers ranging between 2.5 and 5.0. Hamsters were given 0.06 cc. intracerebrally.

Sterility Tests: All tissues and tissue suspensions were routinely cultured on blood agar plates. During the early phases of the work various enrichment mediums as well as plain agar and nutrient broth were employed. Anaerobic cultures were included. No bacterial growth was obtained in any of the mediums, except for occasional contaminants that were encountered especially during the primary isolations.

Filtration: Freshly prepared 10 per cent mouse brain suspensions were centrifuged and put through Berkefeld "V" candles. The bacteria-free filtrates of all four strains of virus produced encephalitis in mice after intracerebral inoculation.

Histologic Studies: Pieces of rabbit cornea and nictitating membrane were fixed in Zenker's solution containing 5 per cent acetic acid and the sections stained with hematoxylin and eosin. Occasionally a mouse brain was cut longitudinally in half and sectioned in the same manner.

Serums: Serums were obtained during the acute phase of the disease and at least a month later, during the convalescent period in all patients except H.T. In addition, a third sample of blood was collected from E.B. approximately three months after the onset of her disease. All serums were removed from the clot as soon as possible and then stored in a box with solid carbon dioxide until used for neutralization tests.

Neutralization Tests: Twenty per cent suspensions of infected mouse brain were prepared each time. Decimal dilutions were made in rabbit serum in isotonic solution of sodium chloride, giving concentrations of 1 to 5, 1 to 50 and so forth up to 1 to 500,000 or 1 to 5,000,000. These when added to equal amounts (0.15 cc.) of undiluted test serums gave final concentrations of 1 to 10, 1 to 100 and so forth up to 1 to 1,000,000 or 1 to 10,000,000. The mixtures of virus dilution and serum were incubated in a water bath for two hours at 37 C. At the end of this time the mixtures were injected intracerebrally into groups of 4 or of 5 mice, which were observed daily for signs of involvement of the central nervous system and death over a period of twenty-one days. LD_{50} titers were calculated according to the method of Reed and Muench,[10] and neutralization indexes were determined by the method described in "Laboratory Methods of the United States Army."[11]

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9. Rabbit serum isotonic solution of sodium chloride consisted of rabbit serum which had been inactivated at 56 C. for one-half hour and made up to 10 per cent in isotonic solution of sodium chloride.

10. Reed, L. J., and Muench, H.: Simple Method of Estimating Fifty per Cent Endpoints, Am. J. Hyg. **27**:493 (May) 1938.

11. Simmons, J. S., and Gentzkow, C. J.: Laboratory Methods of the United States Army, Philadelphia, Lea & Febiger, 1944, p. 591.

Known Strains of Herpes Virus: The H.F. strain of herpes virus [12] was used in most of the immunity tests. The P.A. strain, recently isolated from a patient with herpetic stomatitis, was used in a few of the early tests until the H.F. strain became available.

Disease in Animals: Mice succumbed with symptoms characteristic of herpetic encephalitis after intracerebral or intraperitoneal inoculation. Corneal scarification in rabbits was followed by the typical keratoconjunctivitis of herpes simplex and in many cases by encephalitis.

Isolation of the J.M. Strain.—The crusts and vesicular fluid obtained from J.M. were swabbed on both scarified corneas of rabbit 1. In twenty-four hours violent purulent keratoconjunctivitis was produced in both eyes. At this time the nictitating membrane and cornea of the right eye were removed aseptically and ground in isotonic solution of sodium chloride after representative pieces had been saved for histologic section. Subsequently, when tested for ocular immunity rabbit 1 was observed to be resistant to the P.A. strain of herpes virus.

The nictitating membrane of rabbit 1 was injected intracerebrally into mice and onto the scarified cornea of rabbit 2. This rabbit failed to react. However, the same material produced encephalitis in mice. The cornea of rabbit 1 was transferred to the scarified cornea of rabbit 3. Keratoconjunctivitis developed by the third day. On the seventh day, while the reaction still appeared at its height, the cornea of rabbit 3 was removed and passed to another rabbit, which failed to react. However, herpetic inclusions were readily demonstrated in the cornea of rabbit 3, and it was later shown to be immune to ocular scarification with the P.A. strain of herpes virus.

The brains of all except 1 mouse inoculated with the nictitating membrane of rabbit 1 were discarded because bacteria were observed. A suspension of brain from this mouse was frozen in solid carbon dioxide. Four months later it was thawed and divided into two parts. One part, about 0.5 cc., was left untreated. To the other part, which was approximately 3 cc., 2,500 units of penicillin contained in 0.25 cc. of isotonic solution of sodium chloride was added. Culture of the untreated portion yielded numerous colonies on a blood agar plate, whereas that portion treated with penicillin produced no growth. Both the treated and the untreated portions failed to elicit a response in the scarified corneas of a rabbit immune to the H.F. strain of herpes. On the other hand, passage of both portions to the scarified corneas of a normal rabbit (rabbit 4) evoked severe keratoconjunctivitis. Its nictitating membrane was removed on the third day and injected intracerebrally into 6 mice. Four died with signs of involvement of the central nervous system, while the 2 mice which did not die were resistant five weeks later to the

12. The H. F. strain of herpes simplex was supplied by Drs. P. K. Olitsky and J. Casals of the Rockefeller Institute for Medical Research, New York.

homologous J.M. strain of virus. The original penicillin-treated portion of the mouse brain suspension was injected intracerebrally into 6 mice. All showed signs of encephalitis; 1 died, and 4 were shown to be immune

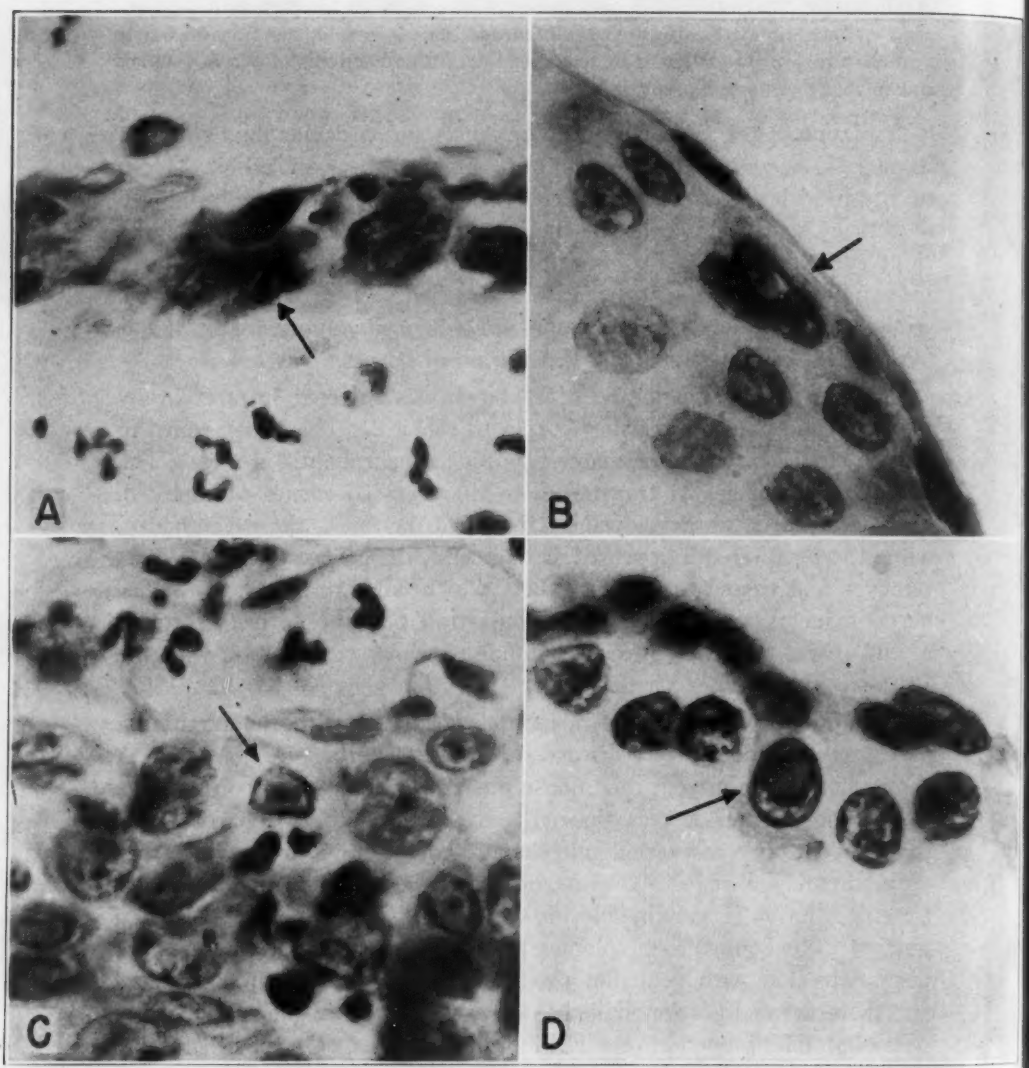

Fig. 2.—Intranuclear inclusions in rabbits' eyes. The sections are stained with hematoxylin and eosin. *A*, intranuclear inclusion in the epithelium of the cornea (case 1) (× approximately 1,297). *B*, intranuclear inclusion in the epithelium of the cornea (case 2) (× approximately 1,297). *C*, intranuclear inclusion in the epithelium of the cornea (case 3) (× approximately 1,297). *D*, intranuclear inclusion in the epithelium of the iris (case 4) (× approximately 1,297).

to herpes. The sixth was killed on the fourth day. Culture of its brain revealed no bacteria, and histologic section showed the presence

of herpetic inclusions. Intracerebral passage of its brain to mice produced convulsions and death between the second and sixth days. Continuous mouse brain passage shortened the period of incubation to as little as twenty-four hours and resulted in a hundred per cent mortality when 10 per cent brain suspensions were employed.

Isolation of the F.R. Strain.—Four small wet vesicles from the skin of patient F.R. were punctured and the contents taken up by a cotton swab and applied to the scarified corneas of rabbit 5. Keratoconjunctivitis developed in rabbit 5, and at seventy-two hours the cornea and nictitating membrane of the left eye were removed. Section of the cornea revealed herpetic inclusions in the epithelial cells. This rabbit was later observed to be immune to ocular infection with the P.A. strain of herpes. Further inoculation of another rabbit with the cornea and nictitating membrane did not produce any reaction. This rabbit was subsequently susceptible to the P.A. strain of virus. Passage of the ground-up nictitating membrane of rabbit 5 to 5 mice resulted in the death of 2 of them on the eighth and ninth days, respectively. Of the 3 remaining animals, 1 was eventually shown to be resistant to cerebral infection with the P.A. strain while another succumbed. The fifth mouse showed symptoms on the eleventh day. The strain obtained from its brain was maintained by continuous mouse brain passage.

Isolation of the E.B. Strain.—Material from cutaneous vesicles and also from the conjunctivas of patient E.B. was inoculated on both eyes of rabbit 8. On the second day when no reaction occurred, fresh material was obtained from a new crop of vesicles and both corneas of the rabbit were reinoculated, as were the corneas of rabbit 9. Severe keratoconjunctivitis developed in the 2 rabbits. Rabbits 8 and 9 were later shown to be immune to ocular infection with the H.F. strain. On the third day following the last inoculation the right cornea and nictitating membrane of rabbit 8 were removed. Section of the cornea showed the presence of eosinophilic intranuclear inclusions in the epithelial cells. The nictitating membrane of rabbit 8 was injected intracerebrally into 5 mice. In 1 encephalitis developed on the eighth day and in another on the tenth day. The brain of the latter was passed to other mice, and this strain was maintained for several passages. The remaining 3 mice were tested about a month later for cerebral immunity to the homologous E.B. strain. One was immune, and the other 2 succumbed.

Recurrence of Eruption in Patient E.B.—Material from the cutaneous lesions of E.B. was inoculated on the corneas of rabbit 10 in the usual manner. Only mild purulent conjunctivitis developed. Although herpetic inclusions could not be demonstrated in either the cornea or nictitating membrane and no disease was produced by cerebral inoculation into mice, the rabbit later resisted both ocular and cerebral

infection with the H.F. strain of herpes. The evidence is therefore inconclusive as to whether herpes virus was present in the lesions of the patient and as to whether this was a true recurrence of the disease.

Isolation of the H.T. Strain.—Swab 1: Material from the lesions of patient H.T. was inoculated on the cornea of 2 rabbits. One, a rabbit which was immune to the H.F. strain of virus, showed no reaction; the other, rabbit 11, showed a characteristic reaction in each eye. The left cornea and nictitating membrane were removed for section and passage on the third day. In the absence of any corneal epithelium no inclusions could be observed. A pool of the nictitating membrane and cornea was passed to rabbit 12 and the nictitating membrane alone to 6 mice. The rabbit, in which a lesion failed to develop, was subsequently susceptible to ocular infection with the H.F. strain. The mice all succumbed between the fifth and seventeenth days after showing signs of involvement of the central nervous system. Herpetic inclusions were demonstrated in sections of the brain of 1 mouse that died on the fifth day. This brain was used to maintain the strain of virus.

On the seventh day rabbit 11 began to show signs of involvement of the central nervous system. The entire right eye was removed and sectioned, and a herpetic inclusion body was observed in the iris. A 20 per cent suspension of the brain was made and injected intracerebrally into 7 mice. One of the mice succumbed on the eighth day, and its brain was used for further passage. The remaining 6 mice remained well and on a later date were shown to be not immune to the homologous strain of virus. A rabbit in which the 20 per cent brain suspension was injected intracerebally had a febrile reaction of three days' duration and then recovered. Four weeks later when this animal's cornea was inoculated with the highly fatal H.F. strain of herpes only mild purulent keratitis developed.

Swab 2: Material for a second inoculation was obtained from patient H.T. the day before death. Keratoconjunctivitis developed in both eyes of the rabbit, and eosinophilic intranuclear inclusions were seen on section. This rabbit was resistant to ocular infection with the known H.F. strain later. Virus was demonstrated in the nictitating membrane by intracerebral subinoculation into 5 mice.

Neutralization Tests.—Two series of neutralization tests were performed. In the first series the patients' serums, obtained during both the acute and the convalescent phase of disease, were studied with regard to their neutralizing effect on the homologous strain of virus, and in the second series the neutralizing effect of the serums from 3 patients on the heterologous H.F. strain of virus was studied. The serum of a normal rabbit was used as a control.

In table 1 it can be seen that J.M. had no antibodies in the serum in the acute phase of the disease, while the serum drawn seven weeks

TABLE 1.—*Results in Mice (Neutralizing Antibodies) of Tests with Patients' Serums (0.03 cc. Injected Intracerebrally)*

Source	Phase of Disease	Date	Homologous Virus Test: Dilution 10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	LD_{50} Titer	N. Index	N. Index Increase	Heterologous (HF) Virus Test: Dilution 10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	LD_{50} Titer	N. Index	N. Index Increase
Normal rabbit	.....	.....	...	4/4†	2/4	3/4	0/4	4.0	....	.....	...	...	3/4	2/4	1/4	5.0	...	....
J. M.	Acute	11/29/45	4/4	4/4	4/4	2/4	...	4.0	1	.....	4/4	4/4	1/4	0/4	0/4	3.7	20	....
J. M.	Convalescent	1/18/46	1/4	1/3	0/4	0/4	...	0.8—	1600+	×1600+	4/4	0/3	0/4	0/4	0/4	2.5	300	×16
Normal rabbit	.....	.....	...	4/5	4/5	2/5	0/5	3.5	....	.....	...	...	...	...	...	...	...	....
F. R.	Acute	1/ 6/46	5/5	4/5	2/5	1/4	...	2.8	5	.....	4/4	3/4	1/4	0/4	0/4	3.5	32	....
F. R.	Convalescent	2/ 6/46	5/5	1/5	1/5	0/5	...	1.7	60	×12	3/4	1/4	0/4	0/4	0/3	2.5	300	×10
Normal rabbit	.....	.....	...	3/4	2/4	0/4	0/4	2.8	....	.....	...	...	...	...	...	...	...	....
E. B.	Acute	2/12/46	0/4	0/4	0/4	0/4	...	0.5—	200+	.....	4/4	2/4	2/4	0/4	0/3	3.5	32	....
E. B.	Convalescent	3/22/46	1/3	0/4	0/4	0/4	...	0.7—	125+	×1	2/4	3/4	0/4	0/4	0/4	3.0	100	× 3
E. B.	Recurrent	5/16/46	1/4	0/4	0/4	0/4	...	0.7—	125+	×1	...	...	...	...	...	...	...	....
Normal rabbit	.....	.....	...	4/4	4/4	2/4	0/4	4.0	....	.....	...	...	...	...	...	...	...	....
H. T.	Acute	4/26/46	4/4	4/4	4/4	0/4	...	3.5	3	.....	...	...	...	...	...	...	...	....

* Neutralization Index = $\frac{LD_{50} \text{ titer normal rabbit serum}}{LD_{50} \text{ titer test serum}}$

† The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

later, during his convalescence, showed a neutralization index of more than 1,600. The serum of F.R. in the acute phase of the disease showed a neutralization index of 5, and the index increased to 60 in the convalescent phase a month later. The neutralization index of the serum of E.B. in the acute phase of the disease was more than 200, and no difference was observed in samples of serum drawn five weeks and three months later, respectively, both indexes being more than 125. No neutralizing antibodies were observed in the serum of H.T., which was drawn just before death.

The neutralization index of the various serums against the heterologous H.F. strain increased during convalescence to a comparable extent. The serum of J.M. during convalescence increased only sixteenfold, as compared to the sixteen hundredfold increase with the homologous strain. The F.R. serum increased tenfold, and the E.B. serum

TABLE 2.—*Cerebral Resistance of Immunized Mice to the H.F. Strain of Herpes Simplex*

Experiment Number	H. F. Suspension Used	Previous Inoculation		Result
		Strain	Route	
1	Rabbit brain (1%)	F. R.....	Intraperitoneal	1/22*
			Intracerebral	0/3
		E. B.....	Intraperitoneal	0/3
			Intracerebral	0/2
		Controls....	.....	6/6
2	Mouse brain (1%)	J. M.....	Intracerebral	0/6
		H. T.....	Intraperitoneal	1/4
		Controls....	.....	10/10

*The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

showed a neglible increase in protective capacity during convalescence, which duplicates the results with the homologous strain. The H.T. serum was not available for neutralization tests with the H.F. strain.

Cross Immunity Tests in Animals.—Final proof of the identity of the infectious agents was established by performing several series of resistance tests in mice, hamsters and rabbits. Mice immunized with the human strains of virus were tested against the H.F. strain, and, conversely, mice immunized with the H.F. strain were tested against the various human strains of virus. A group of hamsters resistant to the H.T. strain also was tested for intracerebral resistance to the H.F. strain. Finally, the experiments were concluded by testing recovered rabbits for ocular immunity to either the P.A. or the H.F. strain of virus.

Cerebral Resistance of Mice to the H.F. Strain: In the first experiment (table 2) mice which had received either the F.R. or E.B. strains

TABLE 3.—*Cerebral Resistance of H.F. Immune Mice to Human Strains of Herpes Simplex*

Experiment Number	Strain of Herpes *	Group of Mice	Result
1	J. M.	H. F. immune	0/4†
		Controls	4/4
2	F. R.	H. F. immune	0.4
		Controls	4.4
3	H. T.	H. F. immune	0/18
		Controls	14/14

* Freshly prepared 10 per cent mouse brain suspensions.

† The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

Note.—In these experiments the H. F. immune mice had survived a previous cerebral challenge with the H. F. strain.

TABLE 4.—*Ocular Resistance of Rabbits to Herpes Simplex*

Experiment Number	Date of Test, Virus Used	Inoculation of Cornea		Reaction	Result
		Strain	Date		
1	1/28/46, P. A. 10% mouse brain	Nonspecific	12/ 4/45	Keratoconjunctivitis, CNS *	
		Nonspecific	12/ 4/45	Keratoconjunctivitis	
		Nonspecific	1/17/46	Keratoconjunctivitis, CNS	
		J. M.	11/29/45	None	Immune
		J. M.	11/30/45	None	Immune
		F. R.	1/ 5/46	None	Immune
2	4/13/46, H. F. 10% rabbit brain	Nonspecific	11/18/45	Keratoconjunctivitis, CNS, D9 †	
		Nonspecific	11/21/45	Keratoconjunctivitis, CNS, D9	
		Nonspecific	3/15/46	Keratoconjunctivitis, CNS, D12 ‡	
		J. M.	1/28/46	None	Immune
		F. R.	1/28/46	None	Immune
		F. R.	2/ 1/46	None	Immune
		E. B.	2/12/46	None	Immune
		E. B.	2/14/46	None	Immune
		E. B.§	3/27/46	None	Immune
3	5/29/46, H. F. 10% mouse brain	Nonspecific	.....	Keratoconjunctivitis, CNS, D8 ‖	
		Nonspecific	5/16/46	Keratoconjunctivitis, CNS, D9	
		J. M.	4/29/46	None	Immune
		H. T.	5/ 2/46	None	Immune
		H. T.¶	5/ 4/46	Mild keratoconjunctivitis	Immune

* Involvement of the central nervous sysem.

† The rabbit died on the ninth day.

‡ The rabbit died on the twelfth day.

§ This rabbit had received material from the recurrent lesions of E. B.

‖ The rabbit died on the eighth day.

¶ This rabbit had received intracerebral injection.

of virus were subjected to an intracerebral injection of a 1 per cent H.F. rabbit brain suspension. All except 1 were solidly immune. In the second experiment a 1 per cent suspension of H.F.-infected mouse brain was employed on mice immune to J.M. and H.T. strains. All except 1 were resistant, thus demonstrating good cross immunity. It may be pointed out that mice which had previously survived a cerebral challenge, regardless of the strain of herpes virus employed, were solidly immune, whereas after previous intraperitoneal injection an occasional mouse succumbed to cerebral inoculation. All control mice in these experiments died.

Cerebral Resistance of Mice Immune to the H.F. Strain to Human Strains of Virus: Freshly prepared 10 per cent mouse brain suspensions were used in these experiments, and the results are listed in table 3. Mice rendered immune to the H.F. strain were resistant to the J.M., F.R. and H.T. strains of virus injected intracerebrally. There were no survivors among the normal controls.

Resistance to the H.F. Strain of Hamsters Immune to the H.T. Strain:—A group of 4 hamsters survived intracerebral injection of the H.T. strain. Later they were all immune to cerebral inoculation with the H.F. strain, while 4 normal controls died.

Ocular Resistance of Rabbits to Strains of Herpes Simplex: Rabbits that had recovered from ocular infection with the four human strains of virus were tested for ocular immunity. Three separate experiments were made and the results are shown in table 4. In the first experiment a 10 per cent suspension of P.A. mouse brain was used. It can be seen that 2 rabbits given injections of J.M. strain and 1 rabbit given the F.R. strain were resistant. In the remaining two tests the H.F. strain became available, and the results showed that good cross immunity was developed in rabbits that had received one of the J.M., F.R., E.B. or H.T. strains of virus. Animals which had been inoculated on the cornea with unrelated materials acted as controls, and all succumbed.

COMMENT

Herpes virus was readily isolated by transfer to a rabbit's cornea from the cutaneous lesions of 4 patients with Kaposi's varicelliform eruption. The infectious agent was obtained in some instances many days after the onset of the disease and once was isolated from the same patient twice, the second time six days after the first. Inclusion bodies were observed in the rabbit's eye on the second day and up to the seventh day after scarification. Intracerebral inoculation of mice with material from infected rabbit's eyes seldom gave universally positive results, but at least in four instances it proved a successful method of transfer when inoculation of single rabbits failed. Antibodies against the homologous herpes virus were absent during the acute phase of the illness

in 3 patients and present in 1. One patient showed a decided rise in titer in the serum in the convalescent period, 1 a slight rise and 1 no rise either after her first illness or after the possible recurrence of the disease. As the fourth patient died, serum was obtained only in the acute period and no antibody was observed. Cross immunity was demonstrated between all four strains and the known H.F. strain and another strain obtained locally from a patient with herpetic stomatitis.

The first suggestion that the disease described by Kaposi might be caused by herpes virus came from the work of Seidenberg,[13] who used material obtained from 2 patients of Esser's [14] to inoculate rabbits. Keratoconjunctivitis developed in the rabbits, and they were subsequently immune to herpes but not to vaccine virus. The excellent work of Wenner [5a] in 1944 established the fact that the virus of herpes simplex is almost certainly the causative agent of the disease. He isolated strains of a filtrable agent from the vesicular fluid of each of 3 infants and from the brain of 1 of them at necropsy and identified the strains as closely related to, if not identical with, the virus of herpes simplex. Serums obtained from 1 patient one month, two months and five months after the onset of illness neutralized herpes virus, but at seven months the antibodies had disappeared. In the serum of a second infant antibodies were observed at eight and at twenty-three days. Blattner and his associates [5c] shortly thereafter reported the recovery from the lesions of a child of a strain of herpes virus by the use of mice and embryonated hens' eggs. Antibodies, absent on the seventh day of illness, were present on the fifteenth and thirtieth days. The patient was 1 of a group of 5 patients reported by Lane and Herold.[15] Serums obtained from the 4 other patients during convalescence and from 1 more patient in Chicago were tested by Blattner for the presence of antibodies. He observed antibodies in the serums of 2 patients of Lane and Herold and in the serum of the patient from Chicago. The serums of the remaining 2 patients were negative. Some doubt existed as to whether 1 of the patients had Kaposi's varicelliform eruption. Lane and Herold gave two possible interpretations of the lack of antibody in the serum of the other patient, who had presented a typical picture of the disease: The disease might have been produced by an unrelated strain of virus, or, in view of the fact that the sample was taken twelve months after recovery, antibodies might have disappeared from the blood stream.

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13. Seidenberg, S.: Zur Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. **4**:398, 1941.

14. Esser, M.: Ueber eine kleine Epidemie von Pustulosis varioliformis acuta, Ann. pædiat. **157**:156, 1941.

15. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption: Report of Five Cases, Arch. Dermat. & Syph. **50**:396 (Dec.) 1944.

Barton and Brunsting [5b] were the first to record the isolation of the herpetic virus from the lesions of an adult. Lynch and his associates [5d] described 4 cases, in 2 adults and 2 infants. Both children were exposed to herpes in their parents, and 1 adult had labial herpes two days prior to his eruption. The fourth patient, aged 54 years, gave no history of exposure. From the lesions of this patient they obtained the virus of herpes simplex. Antibodies were present in the serum of this patient at three days, and there was no change in the titer seventy-five days later. Jaquette and his co-workers [5e] added 1 more proved case in an infant. Although the child had been exposed to a vaccinated sibling, it was the herpetic virus which was isolated from the lesions. Antibodies to herpes absent at the onset were elaborated by the patient during convalescence. Ebert, in a discussion of Lynch's paper, stated that on reexamination of sections of the cornea of a rabbit in which keratitis developed when it was inoculated with material from a patient with Kaposi's eruption, the typical inclusion bodies of the herpes group were seen. He also observed inclusion bodies in the lesions taken from the skin of the patient. Inclusion bodies have been found in the cutaneous lesions of herpes labialis and genitalis.[16] Apparently this is the only instance in which they have been seen in Kaposi's varicelliform eruption.

It is as yet impossible to say whether the herpetic cutaneous eruption is, like herpetic stomatitis, a manifestation of primary herpetic infection.[17] The relative frequency of the disease in infancy and the high fever and prostration of the patients point to such a conclusion. The serums of most of the infants and of some of the adults have been shown to be lacking in antibodies against herpes early in the course of the disease and to develop a rise in titer during convalescence. However, antibodies have been demonstrated in some patients early in the disease; in those patients no rise has subsequently occurred. One patient apparently suffered a relapse [5a] and 1, reported here, a recurrence. The presence of virus in the late lesions was not conclusively demonstrated in either instance. If it is established that Kaposi's varicelliform eruption is a manifestation of primary herpes there will be at least two disease pictures of "herpetic fever": one, the usual herpetic stomatitis and the second, the rarer generalized cutaneous eruption occurring usually on an eczematous base.

16. van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, p. 150.

17. Dodd, K.; Johnston, L. M., and Buddingh, G. J.: Herpetic Stomatitis, J. Pediat. **12**:95 (Jan.) 1938. Burnet, F. M., and Williams, S. W.: Herpes Simplex: New Point of View, M. J. Australia **1**:637 (April 29) 1939.

SUMMARY

Four cases of Kaposi's varicelliform eruption are reported, of which 3 were in adults. One patient had a clinical relapse of the disease thirty-nine days after the first attack, and between these attacks, on the twenty-second day after the first episode, she had labial herpes. Each of these patients had been in contact from five to ten days preceding the onset of Kaposi's varicelliform eruption with 1 or more persons who had labial herpes. The 3 adults had been successfully vaccinated at an earlier date. None of the 4 patients had any known exposure to vaccine virus preceding the development of Kaposi's varicelliform eruption. Penicillin, plasma and immune globulin failed to influence the course of the disease. A filterable agent recovered from the cutaneous lesions of each of these 4 patients was shown by histologic methods and appropriate cross immunity tests in animals to be a strain of herpes simplex virus. An increase in antibodies during convalescence was demonstrated in 2 patients. In 1 fatal case in an adult there were no antibodies in the acute stage.

These 4 cases add corroborative evidence to that already accumulated that Kaposi's varicelliform eruption may be produced by infection with herpes virus in persons having atopic dermatitis. The recovery of the herpes virus distinguishes this disease from eczema vaccinatum, which is due to infection with the vaccine virus in persons having atopic dermatitis.

NOTE.—While this manuscript was in the process of preparation an additional case of Kaposi's varicelliform eruption in a 20 month old infant (male) was diagnosed.[7] Material from the patient's lesions produced keratoconjunctivitis in rabbits, and herpetic inclusions were readily demonstrated in sections of rabbit cornea. A virus recovered from the cutaneous lesions was shown by appropriate immunity tests to be a strain of herpes virus. Antibodies which were absent in the serum in the acute phase of the disease were shown to develop during convalescence. Work is still in progress.

Dr. Roy L. Kile aided in the management of the patients, and Mr. Joseph Homan of the Department of Medical Art prepared the photographs.

ASCORBIC ACID IN THE TREATMENT AND PREVENTION OF POISON OAK DERMATITIS

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THE STUDY of dermatitis venenata due to poison oak (Rhus diversiloba) was undertaken, while I was a member of the armed forces, with the assumption that the manifestations observed in the disease were probably due, as in other allergic states, to an overproduction of histamine and other such monoamines in the body tissues. The hypothesis was carried still further, based on the probability that the irritating factor in poison oak (lobinol, a volatile oil isolated by McNair [1]) first decomposes the protein molecules in the cutaneous tissues into a-amino acids by a process similar to that of the proteolytic enzymes in digestion. These amino acids may further be decomposed not according to the normal method of deamination and oxidation but by losing carbon dioxide from the carboxyl group (decarboxylation) with the formation of a corresponding alkyl amine, as:

$$R\text{-}CH(NH_2)\,COOH \xrightarrow{-CO_2} R\text{-}CH_2NH_2$$

Various studies have shown that the monoamines, such as tyramine and histamine, have a powerful physiologic action even in minute quantities. Histamine, when injected into the body, promptly causes increased arterial tension by its direct action on the arteriolar wall, and later a fall in blood pressure results from increasing capillary permeability. This would probably explain the hyperemia seen in early manifestations of poison oak dermatitis and the subsequent vesiculation of the cutaneous tissue.

An idea was conceived that since one of the physiologic actions of ascorbic acid is to maintain vascular tone, especially of the vascular endothelium, ascorbic acid might counteract the toxic actions of alkyl amines like histamine. An experimental study which I did on rabbits proved this to be true. With this in mind and the knowledge of the harmless effect of ascorbic acid on the human body, a study was undertaken in the treatment and prevention of poison oak dermatitis.

Three hundred and eighty patients with dermatitis venenata due to poison oak were observed and treated by my associates and me. Of

1. McNair, J. B.: Rhus Dermatitis from Rhus Toxicodendron, Radicans and Diversiloba (Poison Ivy): Its Pathology and Chemotherapy, Chicago, University of Chicago Press, 1923.

these, 126 received treatment with ascorbic acid, and the results were favorable. Some of the results were startling, however; obstinate cases of the disease were encountered which necessitated longer treatment, with eventual improvement. The period of treatment was definitely reduced. The average period of treatment for the 126 patients was five days, the shortest two days and the longest ten days (table 1). It was noted that the earlier treatment was initiated after exposure the quicker and more favorable was the recovery. The ascorbic acid was given only to those patients who presented manifestations of moderately severe or severe disease. Patients with mild dermatitis were treated with the usual topical application of calamine lotion or tincture of ferric chloride.

All patients who were treated were ambulant. Few with severe dermatitis had to be hospitalized, and hospitalization in these cases was primarily due to the lack of ascorbic acid at one time or another. It should be remarked that during the period from June to August 1943,

TABLE 1.—*Number of Days Required for Treatment of Each Patient in 126 Cases*

Number of Patients	Days
15	2
28	3
11	4
38	5
11	6
12	7
7	8
4	10

when more than two thirds of the 380 patients were treated, only 6 were hospitalized. In 1 of these a secondary infection had developed.

In the determination of prophylaxis against poison oak dermatitis, two groups of men (24 in each group) who were sensitive to the plant were employed as test cases. Each group was divided into two sections, 12 men in each section. During the period of exposure to poison oak, those in one section took the prescribed prophylactic dose of ascorbic acid and those in the other did not. Those who took the prophylactic dose of ascorbic acid did not contract the disease when exposed, while a large percentage of those who were not given the daily dose of ascorbic acid did contract poison oak dermatitis, ranging from mild to severe (tables 2 and 3). The dose which is felt to be adequate for protection ranges from 150 to 300 mg. daily and can be taken in tablet form, in divided doses. This daily dose must be taken one day prior to exposure, every day during exposure and at least twenty-four to forty-eight hours after exposure.

The dosage varied somewhat and depended on the severity of the dermatitis. However, it is felt that the maximum daily dose in any

case is 600 mg. of ascorbic acid. The dose was divided into two or three portions during the day and given at intervals of four to six hours. Sterile ampules of ascorbic acid solution, 100 mg. each, were employed. It is believed that a more concentrated solution or a preparation of a

TABLE 2.—*Results of Prophylaxis Against Poison Oak* in Group 1†*

Section A‡		Section B§	
Case No.	Resultant Dermatitis	Case No.	Resultant Dermatitis
1	None	13	Mild
2	None	14	Mild
3	None	15	Severe
4	None	16	Moderate
5	None	17	Moderate
6	None	18	Moderate
7	None	19	None
8	None	20	None
9	None	21	Mild
10	None	22	None
11	None	23	Moderate
12	None	24	Moderate

* The patient in each case gave a history of being highly susceptible to poison oak.

† Investigation was made along the California coast line.

‡ These patients were given 300 mg. of ascorbic acid by mouth daily, in divided doses of 100 mg. each, during a period of exposure of three days and were checked on the fifth day for signs of poison oak dermatitis.

§ These patients received no ascorbic acid, were exposed for three days and were checked for signs of poison oak dermatitis on the fifth day.

TABLE 3.—*Results of Prophylaxis Against Poison Oak* in Group 2†*

Section A‡		Section B§	
Case No.	Resultant Dermatitis	Case No.	Resultant Dermatitis
25	None	37	Moderately severe
26	None	38	Moderate
27	None	39	Severe
28	None	40	Moderate
29	None	41	Severe
30	None	42	Moderate
31	None	43	Severe
32	None	44	Severe
33	None	45	Moderate
34	None	46	Moderate
35	None	47	Moderately severe
36	Moderate‖	48	Moderate

* The patient in each case gave a history of being highly susceptible to poison oak.

† Investigation was made along the California coast line.

‡ These patients were given 150 mg. of ascorbic acid by mouth daily, in divided doses of 50 mg. each, for a period of seven days. Exposure began on the second day after the initiation of prophylaxis and lasted for five days. On the seventh day they were examined for signs of dermatitis.

§ These patients received no ascorbic acid, and the period of exposure and time of examination were as for section A.

‖ The patient in this case did not follow the prescribed procedure.

water-in-oil emulsion of ascorbic acid, for prolonged action would serve the purpose more satisfactorily. The best route of injection seems to be the intramuscular one, for if given intravenously the ascorbic acid is eliminated too rapidly from the blood stream. The subcutaneous method

is too painful. It is also advisable under certain conditions to give the ascorbic acid in tablet form by mouth as a supportive to the injection. When ascorbic acid is given orally, twice the amount that is employed by injection should be given. This, however, does not completely replace the injections. When vesiculation is present topical application of calamine lotion is recommended as a supportive measure.

At no time were deleterious effects from the drug observed. In fact, patients usually said that they felt well while taking the ascorbic acid.

The drug may be given up to 1 Gm. or more daily. The first sign of improvement is a reduction in itching. This may come about two to four hours after the first injection. This improvement wears off in a few hours if no further ascorbic acid is given. That is probably due to the fact that the ascorbic acid is rapidly eliminated from the system. Furthermore, in no instance were there noted any inflammatory reactions, which are at times seen when extracts of poison oak preparations are given.

SUMMARY

Despite the small number of patients treated and the diverse reactions of different persons to poison oak and to treatment, which make it difficult for one to reach concise conclusions, it is felt that ascorbic acid is capable of combating the disease. Through its physiologic action it has possibilities in preventing the contraction of poison oak dermatitis, and it promptly alleviates the symptoms of the already contracted disease. The best results are usually obtained in those persons who present symptoms of edema, as of the eyelids and genitals.

NOTE.—The author was awarded the Commendation Ribbon by the War Department for meritorious service, while a member of the 125th Infantry, Northern California Sector, in 1943. The commendation stated "Colonel (then Captain) Klasson conducted an investigation and study on the cause and cure of poison oak, the results of which were applied with commendable success within the regiment, thereby contributing greatly to the health and comfort of the command."

80 Clarkson Avenue.

Clinical Notes

TROPICAL LICHENOID DERMATITIS

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JOHANNESBURG, UNION OF SOUTH AFRICA

The submission of this note is prompted by a recent article by Nelson.[1] During 1944 and the early part of 1945, patients presenting the syndrome later described by Bagby[2] and Nisbet[3] were frequently seen in the Italian theater of war, and their cases were discussed by Nelson with the dermatalogists mentioned in his first reference. I had over 50 cases at 102 South African General Hospital in Bari and was able to see several more at the neighboring New Zealand General Hospital. These facts alone would not justify the further report of a disease which has now been adequately described, but I feel that the following points might be of historical interest:

1. In 1935, while I was stationed in Soroti, Uganda, British East Africa, I saw a colleague's wife with a cutaneous disease which resembled acute lichen planus, which diagnosis had been made by Dr. J. H. Sequeira (then practicing in Nairobi, Kenya Colony). This woman and her husband were, to my knowledge, the first persons in Uganda to take "atebrin" (quinacrine hydrochloride)[4] for the suppression of malaria instead of the standard quinine compound.

2. In February 1944, during a discussion at the Section of Dermatology of the Royal Society of Medicine, Major Hellier and Dr. Roxburgh between them mentioned 3 cases of atypical lichen planus in soldiers from West and North Africa.[5] They stressed the occurrence of facial lesions, and it was the appearance of this "spectacle frame" dermatitis in many of the patients seen by Nelson and me that suggested to my mind a common factor between the case herein mentioned, 3 cases from West and North Africa and the numerous cases which were being seen in the Italian theater. The only common factor which occurred to me was the taking of quinacrine hydrochloride, and it was then that I first suggested that this drug might be of causative significance. Apparently, the same idea occurred inde-

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1. Nelson, L. M.: Unusual Dermatosis Simulating Lichen Planus and Lichen Cornens Hypertrophicus: Report of Six Cases, Arch. Dermat. & Syph. **55**:12 (Jan.) 1947.

2. Bagby, J. W.: A Tropical Lichen Planus-like Disease, Arch. Dermat. & Syph. **52**:1 (July) 1945.

3. Nisbet, T. W.: A New Cutaneous Syndrome Occurring in New Guinea and Adjacent Islands, Arch. Dermat. & Syph. **52**:221 (Oct.) 1945.

4. The original German product is referred to here.

5. Hellier and Roxburgh, A. C., in discussion on Dowling, G. B.: Erythematous Lichen Planus, Proc. Roy. Soc. Med. **37**:410 (June) 1944.

pendently to Peterkin.[6] The War Office, however, vetoed the proposed publication of these cases.[3] I had previously submitted to the editor of this journal a short article on a case of sensitization to actinic light which was precipitated by quinacrine hydrochloride and had mentioned that this was apparently unconnected with a series of cases of lichen planus attributable to the drug. In view of the veto by the War Office I asked the editor not to publish the report.

CLINICAL COMMENT

Two points might conveniently be mentioned here: 1. In none of the cases observed by me were there lesions of the glans penis, although the oral mucosa was frequently involved. This would be a remarkable fact were the disease true extensive lichen planus. Bazemore and his colleagues[7] did not mention lesions of the glans penis in over 400 cases of this disease which were seen by them. This fact might be of importance in the differential diagnosis. 2. In 1 case seen by me the eruption began as large bullae, which appeared on apparently normal skin. Only after these bullae had ruptured and healed did lichenoid lesions appear, on both previous sites of bullae and previously unaffected areas.

SUMMARY

A historical retrospect of tropical lichenoid dermatitis includes a case seen by me in 1935. Attention is drawn to the absence of lesions of the glans penis.

64 Moray House, Jeppe Street.

6. Peterkin, cited by Nelson.[4]

7. Bazemore, J. M.; Johnson, H. H.; Swanson, E. R., and Hayman, J. M.: Relation of Quinacrine Hydrochloride to Lichenoid Dermatitis (Atypical Lichen Planus), Arch. Dermat. & Syph. **54**:308 (Sept.) 1946.

SULFONAMIDE SENSITIVITY AND PROPHYLAXIS AGAINST VENEREAL DISEASE

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LITTLE ROCK, ARK.

The soldier in the recent conflict was exposed to sulfonamide drugs in many forms in his appearances at the unit dispensaries. The various forms of toxic cutaneous reactions to these drugs have been adequately dealt with by Cohen, Thomas and Kalisch,[1] Weiner,[2] Ellis[3] and others, and the following case is reported in order to show that small amounts of the drug may set off irritating and extensive reactions.

Prophylaxis against venereal disease as practiced in the army was of several types. The "station" type of prophylaxis at the dispensaries consisted of local

1. Cohen, M. H.; Thomas, H. B., and Kalisch, A. C.: Hypersensitivity Produced by the Topical Application of Sulfathiazole, J. A. M. A. **121**:408 (Feb. 6) 1943.

2. Weiner, A. L.: Cutaneous Hypersensitivity to Topical Application of Sulfathiazole, J. A. M. A. **121**:411 (Feb. 6) 1943.

3. Ellis, F. A.: The Potential Danger of the Topical Use of Sulfathiazole, South. M. J. **37**:493 (Sept.) 1944.

use of soap and water, intraurethral instillation of strong protein silver solution and local application of ointment of mild mercurous chloride. For areas where station facilities were not convenient the soldier was furnished with an individual chemical prophylactic kit. The earlier types of these packets contained two tubes of silver trinitrophenolate and ointment of mild mercurous chloride; another type was of silver preparation. Later a one tube kit was issued which contained 15 per cent sulfathiazole and 30 per cent ointment of mild mercurous chloride. The latter type was responsible for a typical toxic cutaneous reaction in the case described.

REPORT OF A CASE

A white soldier, aged 24 years, was first seen in the dispensary in August 1943, for a complaint of penile sores following sexual contact. A diagnosis of chancroid was made, and the treatment included the use of 7.5 grains of sulfathiazole three times daily. To the patient's knowledge he had not previously had any sulfonamide drugs. Treatment was continued until the afternoon of the following day, when there appeared generalized edema of the face, which closed the eyelids, pruritus, erythema and formation of vesicles about the lips and chin and edema of the hands. The vesicles became enlarged, coalesced and contained moderate amounts of a clear fluid. No other symptoms were noted. The lesions rapidly disappeared after treatment with the drug was discontinued. In November 1944 the patient reported to another dispensary, with a urethral discharge subsequently diagnosed as acute gonorrheal urethritis. Treatment was instituted with 2 Gm. of sulfathiazole, since the patient made no mention of his sensitivity, and within four hours the same phenomena appeared as on the previous occasion: edema, erythema and formation of blebs about the face and lower lip. Penicillin was substituted, and the patient rapidly improved. He was cautioned for a second time about his sensitivity. In May, 1945, following another contact, acute gonorrheal urethritis was again diagnosed, and 500,000 units of penicillin were required before the discharge ceased. On July 14 the patient had another sexual contact, and twenty minutes later he used an individual chemical prophylactic kit of the type described as containing sulfathiazole. After five to six hours the following reaction was noted: pruritus of the face, edema of the lips and the soft tissues about the eyes and vesicles about the upper lip and cheeks. No local lesions were noted about the genitals, and in this instance the symptoms were not as severe as on the previous occasions. Recovery was complete in thirty-six hours with no treatment. Questioning revealed that on numerous other occasions when chemical prophylaxis was used the method was always of the "station" type or with the two tube silver packets (trinitrophenolate and ointment of mild mercurous chloride). After this last episode patch tests were made with 5 per cent sulfathiazole and sulfadiazine ointments, and each elicited a strong erythematous reaction. Minute vesicles were noted with sulfathiazole. Ointment of mild mercurous chloride gave no reaction.

CONCLUSIONS

This case exemplifies the fact that after sensitization to a sulfonamide compound once occurs later exposures to the same drug can produce identical reactions, regardless of whether the drug is taken orally or applied to a cutaneous or mucous surface. Abramowitz [4] and Lane [5] have indicated that the commonest offender

4. Abramowitz, E. W.: Hazards of the External Use of Sulfonamide Compounds, Arch. Dermat. & Syph. **50**:289 (Nov.) 1944.

5. Lane, C. W.: Observations on the Topical Application of the Sulfonamides, South. M. J. **38**:125 (Feb.) 1945.

is sulfathiazole in topical application, although the other members of the group are almost equally frequently a cause. Certainly the use of the drugs internally for more serious illnesses poses a sufficiently large problem for the prescriber of these drugs. It would seem to be a questionable policy to have a chemical prophylactic kit containing sulfonamide compounds available to the public for mass and indiscriminate use.

TREATMENT OF SCABIES WITH DDT (DICHLORODIPHENYLTRICHLOROETHANE)

MAJOR LAWRENCE C. GOLDBERG
MEDICAL CORPS, ARMY OF THE UNITED STATES

War and scabies go hand in hand, and so the detection and treatment of scabies in returning soldiers are important. The period of incubation of scabies is about three weeks. Although the disease may have been contracted in India, China, France or Italy, it may not be evident until after the soldier has landed in the United States because of the speed of modern travel. The zeal to see his sweetheart, wife or family may overshadow the "itch," and thus the soldier innocently spreads the infection to a large number of persons by various means, such as riding buses and trains, sleeping in hotels and private homes and sexual intercourse. Though the number of cases seen in an army general hospital nowhere compares with that seen overseas or in large camps, there are enough to constitute a therapeutic problem. Incidentally, it appeared to me that there were proportionately many more cases from the Mediterranean and European theaters than from the Pacific and allied theaters of operations. During a six month period of observation 307 cases of scabies were diagnosed at Oliver General Hospital; 80 per cent of the patients had no symptoms or eruption until after their arrival in the zone of the interior.

There are numerous methods of treating scabies. Each gives good results but may have certain undesirable qualities. The use of salves is messy and uncomfortable. Benzyl benzoate is effective, but about 10 to 15 per cent of patients treated with it have untoward reactions, particularly dermatitis venenata. With practically all methods there is about 5 to 10 per cent relapse after treatment. About the same percentage of patients are careless in following a prescribed treatment. It therefore appeared that there was still room for improvement in the treatment of scabies. Though others may have used the method to be reported, no articles to date have appeared on the subject.

A prescription for a lotion containing DDT (dichlorodiphenyltrichloroethane), a lotion being considered more desirable than a salve in that it can be applied more freely and quickly, was devised which it was hoped would be harmless and without side effects. This was done hesitatingly, since it had been reported that DDT was harmful to the skin and particularly injurious if applied in an oily solution and since it was reported to be easily absorbed and capable of causing changes in the blood cells and the viscera. A 7 per cent mixture of DDT in equal parts of xylol, ether and liquid petrolatum was prepared, and I used it on myself as a repellent for mosquitoes for two weeks. Since there were no unpleasant effects, it was given to patients to be applied to the body once a

From Oliver General Hospital, Augusta, Ga.

day for three days, and the first 10 patients were studied for changes in the blood and urine. Since no changes were seen in red or white cells, platelets, hemoglobin or urine more persons were treated both at this installation and at several larger camps. No ill effects were reported, and in better than 95 per cent of the patients the pruritus disappeared after the first application. Though not all the cases could be followed there was only about 6 per cent failure after the three day treatment. It appears that if the clothing and bed linens could have been washed in a DDT solution the recurrence of the scabies could have been still further reduced. Treatment with DDT in the form of inert powder or salve was not attempted. Again, some of the relapses were due to the fact that many of the patients were treated while in arm, leg or partial body casts, and the parasites were still under the casts after treatment. The desire to relieve them of some of their nocturnal pruritus was the reason for treatment. A group of patients with scabies was treated with only the mixture of xylol, ether and liquid petrolatum, but they failed to respond to treatment. The average patient used about 240 to 300 cc. of solution.

SUMMARY AND CONCLUSIONS

Soldiers have returned and are still returning from overseas, infested with scabies. Because of this, physicians should be alert to a higher incidence of scabies in the civilian population. In a six month period, 307 patients with scabies at Oliver General Hospital have been successfully treated with a 7 per cent solution of DDT (dichlorodiphenyltrichloroethane) in equal parts of xylol, ether and liquid petrolatum. The lotion is applied once a day for three days, and the average patient uses between 240 and 300 cc. of fluid. The usual procedures of changing and cleaning clothes and bedding are recommended. Spraying or rinsing the clothes in a 5 to 7 per cent DDT solution might further decrease the incidence of relapse or infestation. No untoward symptoms, such as dermatitis venenata or changes in the blood elements or urine, were observed. No doubt, as with all drugs, there will be some untoward reactions, but to date none has been noted. Ninety-five per cent of the patients treated did not experience pruritus after the first treatment. Six per cent of the patients required further courses of treatment. Though this is not a large series of cases and many could not be followed for long periods of time to permit my drawing any final and definite conclusions, I believe that DDT will figure importantly in the treatment of scabies.

623 Doctors Building.

Obituaries

WALTER THOMPSON GARFIELD, M.D.

1882-1947

Walter Thompson Garfield, one of the older members of the New England Dermatological Society, died following a cerebral hemorrhage on May 30, 1947. He leaves his widow and two sons, Leonard Dwinell and Philip Nickerson.

Garfield was born in Pembroke, Mass., on Feb. 8, 1882, the son of Leonard Dwinell and Leonice Thompson Garfield. His early education was obtained at the Cambridge Latin School, from which he graduated in 1902. He received the degree of A.B. from Harvard College in 1906 and the degree of M.D. from the Medical School in 1909.

After internship at the Boston City Hospital he practiced general medicine from 1912 to 1917. He served as Assistant Superintendent of the Bailey Hospital at Lincoln, Neb., and at St. Elizabeth's Hospital at Washington, D. C. He served in World War I from 1917 to 1919 as a captain in the Medical Corps. After his return he practiced dermatology and syphilology and was connected with the Boston City Hospital and the Boston Dispensary as a visiting physician.

He became Chief of the Dermatological Service of the Boston City Hospital during the recent war and was connected with Tufts College Medical School as a teacher from 1921 to 1944, when he became Professor of Dermatology and Syphilology.

He was a diplomate of the American Board of Dermatology and Syphilology and a member of the American Academy of Dermatology and Syphilology and of the New England Dermatological Society, of which he was a past president. He was Chief of the Outpatient Clinic in Dermatology, Cambridge City Hospital, and a consulting physician at the Norwood and Long Island Hospitals at the time of his death.

He was a member of Mt. Olivet Lodge, Ancient Free and Accepted Masons, from 1902 to 1947 and a thirty-second degree member of the Albert Pike Consistory of Washington, D. C., from 1918 to 1927. He was a member of the Utopian Club and past president of the Sachem Council Boy Scouts of America.

Garfield was of a retiring and modest nature, but friendly with those with whom he was associated in his professional life. He served in the various dermatologic clinics with kindly consideration for the underprivileged patients from the poorer districts served by these clinics.

In the clinic he was always punctual in his attendance and carried out his duties with diligence and thoroughness.

Dr. Garfield was a keen clinical observer and a good diagnostician, and his discussion of cases was always interesting. He made many contributions to dermatologic literature over the years and presented a variety of interesting cases at the clinical meetings of the New England Dermatological Society.

Dr. Garfield will be missed by the New England Dermatologists and particularly by his patients who recognized in him a skilful and kindly physician.

WILLIAM P. BOARDMAN, M.D.

News and Comment

GENERAL NEWS

Application for Space in Scientific Exhibit at Next Annual Session.—The Scientific Exhibit for the next annual session of the American Medical Association, to be held in Chicago in June 1948, is under the direction of Dr. Francis W. Lynch, 1466 Lowry Medical Arts Building, St. Paul. Those who desire to present an exhibit should write directly to Dr. Lynch for application for space.

INDEX TO VOLUME 56

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Biographies, Book Reviews, Editorials, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, E, O and S, respectively.

Abnormalities and Deformities: See under names of diseases, organs and regions, as Atrophy; Hair; Pigmentation; Skin, abnormalities; etc.
Abscess: See under names of organs and regions, as Nails; etc.
Acariasis; cheese mite dermatitis, 405
Acarus Scabiei: See Scabies
Achromia: See Pigmentation; Vitiligo
Acid; acidity of scalp; nature and possible relation to seborrhea, *448
action of soap on skin; action of soap containing little or no lauric or oleic acid, *419
Ascorbic: See Ascorbic Acid
Cevitamic: See Ascorbic Acid
fatty; propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601
Nicotinic: See Nicotinic Acid
Undecylenic: See also Moniliasis; Ringworm; Skin, diseases
undecylenic; clinical evaluation as fungicide [desenex], *256
Acne rosacea; vitamin B complex deficiency, *589
treatment of undermining acne lesions by exteriorization, *7
vulgaris; cutaneous diseases of special significance to Air Force personnel, *370
vulgaris in tuberculous patients, *64
Acridine Dyes; atypical lichen planus (dermatitis medicamentosa due to quinacrine [atabrine]), 127
atypical lichenoid dermatitis; drug eruption due to quinacrine hydrochloride (atabrine), *13
Acrodermatitis pustulosa perstans (so-called pustular psoriasis), *766
Acrokeratosis: See Keratosis
Acrosclerosis: See Scleroderma
Actinic Rays: See Roentgen Rays
Actinodermatitis: See under Light; Roentgen Rays
Actinomycosis, primary, of skin; report of case, *706
Addison, M. J.: Reticuloendotheliosis (Letterer-Siwe disease), 122
Adenoacanthoma of sweat glands; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
Adenoma sebaceum (Pringle), 130
Adipose Tissue: See Lipoma
Aeronautics: See Aviation and Aviators
Age, Old: See Old Age
Alcohol; simple plastic mount for permanent preservation of fungi and small arthropods, *763
Alden, H. S.: Atypical lichenoid dermatitis; drug eruption due to quinacrine hydrochloride (atabrine), *13
Alkali; cosmetic dermatology; alkalinity of face powder mixtures, *666
Allergy: See Anaphylaxis and Allergy
Allington, H. V.: Cutaneous reactions to penicillin, *325
Alopecia: See also under Hair
cicatrisata (pseudopelade), 130
congenital hypotrichosis and keratosis pilaris; case for diagnosis, 278
otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379
American Academy of Dermatology and Syphilology, application for space in scientific exhibit, 138, 282
American Medical Association, application for space in scientific exhibit at next annual session, 714, 874
Amersbach, J. C.: Metastatic basal cell epithelioma; report of case, *172
Aminophylline: See Pruritus
Anaphylaxis and Allergy: See also under names of various diseases, as Eczema; Rhus; etc.
contact eczematous dermatitis and patch tests; histologic study, *678
eczematous sensitization; review of its immunologic properties and some speculations as to its nature, *222
Anderson, N. P.: Cheese mite dermatitis, 405
Erythema multiforme (recurrent) with herpes simplex, 117
Squamous cell epithelioma developing in nevus, 113
Androgens; otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379
Angiokeratoma; hemangiomas of scrotum (angiokeratoma of Fordyce?), 399
Anhidrosis: See Sweat Glands
Aphthae: See Stomatitis
Apparatus: See Instruments
Aquaphor: See Cholesterol
Arday, E. J.: Nevus pigmentosus et pilosus, 127
Armies: See Aviation and Aviators; Military Medicine; War
Aron, H. C. S.: Prenatal syphilis; its prevention by use of penicillin in treatment of pregnant women with early infectious syphilis, *349
Arsenic and Arsenic Compounds: See also Arsphenamines
biologic evaluation of vehicles for external application of BAL, *90
relation between thiamine and arsenical toxicity; preliminary report, *634
suppression of treponemicidal action of arsenic with 2,3-dimercaptopropanol (BAL); report of clinical observations in 5 cases, *695
Therapy: See Syphilis
Arsphenamines; ninth day erythema showing photosensitivity, *771
Arthritis; Reiter's disease; comparison with keratosis blennorrhagica and with psoriasis arthropathica, *191
Arthropods; simple plastic mount for permanent preservation of fungi and small arthropods, *763
Ascorbic Acid in treatment and prevention of poison oak dermatitis, *864
Asthma: See Anaphylaxis and Allergy
Atabrine: See Acridine Dyes
Athlete's Foot: See Ringworm
Atopy: See Anaphylaxis and Allergy
Atrophoderma: See Atrophy
Atrophy: See also Poikiloderma atrophicans vasculare; and under names of organs and regions
diffuse idiopathic, of skin associated with advanced pulmonary tuberculosis, 279
Aviation and Aviators; cutaneous diseases in Army Air Force personnel, *364

Avitaminoses: See under Vitamins
Axilla, Lymph Nodes: See Lymph Nodes
Ayres, S., Jr.: Multiple benign cystic epithelioma, 120
Multiple lipoma, 118
Otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379

BCG: See under Tuberculosis
Bacteria: See Streptococci; etc.
Calmette-Guérin: See Tuberculosis
Diphtheria: See Diphtheria
Leprosy: See Leprosy
Baer, R. L.: Biologic evaluation of vehicles for external application of BAL, *90
Extensive Trichophyton purpureum infection, with nevoid anomaly of skin; report of case, together with mycologic and physiologic studies, *834
BAL: See Arsenic and Arsenic Compounds
Balanitis: See Penis
Baldness: See Alopecia
Bancroft, I.: Superficial, erythematous basal cell epithelioma, 121
Barefoot, S. W.: Effects of roentgen ray irradiation on testes of rabbits; possible harmful effects on human testes from low voltage roentgen ray therapy, *471
Barr, J. H., Jr.: Dermatitis repens, 124
Late chronic lymphogranuloma venereum with elephantiasis, 125
Pemphigus foliaceus, 123
Bartlett, A. G.: Extragenital chancre of ear, *264
Barton, R. L.: Granuloma inguinale treated with streptomycin; report of 3 cases, *1
Prenatal syphilis; its prevention by use of penicillin in treatment of pregnant women with early infectious syphilis, *349
Therapy of early syphilis with massive doses of penicillin, *339
Bauer, T. J.: Granuloma inguinale treated with streptomycin; report of 3 cases, *1
Prenatal syphilis; its prevention by use of penicillin in treatment of pregnant women with early infectious syphilis, *349
Therapy of early syphilis with massive doses of penicillin, *339
Bazin's Disease: See Erythema induratum
Bechet, P. E.: Howard Fox; leader in medicine and great dermatologist, *560
Benteen, H.: Treatment of undermining acne lesions by exteriorization, *7
Bereston, E. S.: Treatment of undermining acne lesions by exteriorization, *7
Bergeim, O.: Acidity of scalp; nature and possible relation to seborrhea, *448
Berlin, C.: Ninth day erythema showing photosensitivity, *771
Besnier-Boeck's Disease: See Sarcoidosis
Binkley, G. W.: Recalcitrant pustular eruption on extremities, 124

Biographies:
Fox, Howard, *560

Biology; biologic evaluation of vehicles for external application of BAL, *90
Birthmark: See Nevi
Bismuth and Bismuth Compounds, Therapy: See under names of various diseases, as Neurosyphilis; Syphilis; etc.
Blank, H.: Treatment of plantar warts, *459
Blank, I. H.: Action of soap on skin; action of soap containing little or no lauric or oleic acid, *419
Blastomycosis: See also Moniliasis
North American type; proved case from European Continent, *529
Blisters: See Vesication
Blood, chemistry of palmar sweat; chloride, *462
chemistry of palmar sweat; reducing substances (glucose), *819
chemistry of palmar sweat; urea, *827
Diseases: See Leukemia
Vessels: See also Endarteritis; Periarteritis; etc.
vessels; ulcerating hemangioblastoma; report of case, *506
Bloom, D.: Congenital hypotrichosis and keratosis pilaris; case for diagnosis, 278
Myoblastoma; report of case of myoblastoma of lip followed by multiple tumors of skin, *648
Bluefarb, S. M.: Comedos following roentgen ray therapy, *537
Boardman, W. P.: Walter Thompson Garfield, 873
Boeck's Sarcoid: See Sarcoidosis
Bones: See also under names of bones
metaplasia; report of case, *536

Book Reviews:
Atlas of Commoner Skin Diseases; H. C. G. Semon, 137
Atlas of Histopathology of Skin; G. H. Percival, A. M. Drennan and T. C. Dodds, 556
Control of Venereal Diseases; R. A. Vonderlehr and J. R. Heller Jr., 137
Modern Dermatology and Syphilology; S. W. Becker and M. E. Obermayer, 558
Penicillin in Syphilis; J. E. Moore, 557
Skin Reactions Caused by Fractions of Oil of Turpentine and Hexanitrodiphenylamine: Experimental Investigations by Means of Adhesion Chamber Method; I. Rokstad, 138
Studies on Acarus Scabiei and Scabies; B. Heilesen, 406
X-Ray Treatment of Accessible Cancer; D. W. Smithers, 282
X-Rays and Radium in Treatment of Diseases of Skin; G. M. MacKee and A. C. Cipollaro, 406

Bostick, W. L.: Histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Botryomycosis Hominis: See Granuloma pyogenicum
Bouillaud's Disease: See Rheumatic Fever
Brain, Syphilis: See Neurosyphilis
Breast; melanoma of nipple, 113
Brill, F. A., Jr.: Correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Brocq's Disease: See Alopecia cicatrisata
Brody, M.: Blastomycosis, North American type; proved case from European Continent, *529
Brooke-Morrow's Disease: See Keratosis follicularis
Brunauer, S. R.: Vitamin A in Darier's disease, *306
Bubo, Climatic: See Lymphogranuloma Venereum
Bullosis: See Vesication
Bundesen, H. N.: Therapy of early syphilis with massive doses of penicillin, *339
Burger, R. A.: Sulfonamide sensitivity and prophylaxis against venereal disease, *869
Burkhart, R. J.: Tinea capitis, *111
Buschke's Disease: See Scleroderma

Calcification; scleroderma; tropic ulcers; calcified ganglion of tendon sheath, 544
Calcinosis: See Calcification
Callaway, J. L.: Effects of roentgen ray irradiation on testes of rabbits; possible harmful effects on human testes from low voltage roentgen ray therapy, *471
Callosities: See Keratosis
Calmette-Guérin Vaccine: See Tuberculosis

Cancer: See also Epithelioma; Sarcoma; and under names of organs and regions, as Face; Sweat Glands; etc.
metastases; metastatic basal cell epithelioma; report of case, *172
Candida: See Moniliasis
Canizares, O.: Cutaneous diseases in Army Air Force personnel, *364
Dermatitis venenata due to streptomycin, *676
Capillaries: See Blood vessels; Vasomotor System
Caplin, S. M.: Simple plastic mount for permanent preservation of fungi and small arthropods, *763
Caprylate: See Mycosis, cutaneous
Carcinoma: See Cancer
Cardiovascular System: See Blood vessels; Vasomotor System; etc.
Carney, R. G.: Acquired loose skin (chalazodermia); report of case, *794
Caro, M. R.: Psoriasis of hands, nonpustular type, *629
Role of clinician in modern dermatology; president's address, *283
Cattle, suppurative ringworm contracted from, *780
Cautery drainage of subungual abscess, *269
Cells: See also Tissue; etc.
adenoacanthoma of sweat glands; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
granular cell myoblastoma; report of 2 cases, *812
Cerebrospinal Fluid, observations in lymphogranuloma venereum, *699
Cevitamic Acid: See Ascorbic Acid
Chalazodermia: See Skin, abnormalities
Chancre, extragenital, of ear, *264
Lymphogranulomatous: See Lymphogranuloma Venereum
Chaulmoogra Oil, Therapy: See Leprosy
Cheese Mite: See Acariasis
Cheilitis: See Lips, diseases
Chemosurgery: See Face
Chemotherapy: See under names of diseases and chemotherapeutic agents, as Neurosyphilis; Penicillin; Sulfonamides; Syphilis; Tuberculosis; etc.
Chloroma: See Leukemia
Cholesterol; allergic contact dermatitis due to wool fat and cholesterol, *801
Church, J. M.: Cutaneous diphtheria; report of 10 cases, *357
Cipollaro, A. C.: Granular cell myoblastoma: report of 2 cases, *812
Psoriasis; case for diagnosis, 274
Clinician, role in modern dermatology; president's address, *283
Clothing: use of sock as elbow dressing, *535
Coal Tar in dermatology; improvement in its physical properties without any change in its therapeutic action, *583
Cohen, W.: Failure of resin of podophyllum in treatment of verruca vulgaris, *109
Cole, H. N.: Atypical lichen planus (dermatitis medicamentosa due to quinacrine [atabrine]), 127
Dermatitis repens, 124
Pemphigus foliaceus, 123
Colitis, ulcerative, pyoderma gangrenosum in; report of case, *187
Collins, W. T.: Disseminated ulcerating sporotrichosis with widespread visceral involvement, *523
Colloidal Gold Sulfide: See Lupus erythematosus
Colon, Inflammation: See Colitis
Combes, F. C.: Coal tar in dermatology; improvement in its physical properties without any change in its therapeutic action, *583
Comedos following roentgen ray therapy, *537
localized in temporoxygomatic area, *376
Communicable Diseases: See Syphilis; etc.
Complement-Fixation Reaction: See under Syphilis
Condyloma; effects of resin of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, *30
Congress: See Societies
Conjunctivitis, contact cheilitis and stomatitis from use of penicillin, *327
Reiter's disease; comparison with keratosis blennorrhagica and with psoriasis arthropathica, *191
Corn Starch: See Starch
Cornbleet, T.: Acidity of scalp; nature and possible relation to seborrhea, *448
Corson, E. F.: Long Hair, chief of Crows, *443
Use of sock as elbow dressing, *535
Corynebacterium Diphtheriae: See Diphtheria
Cosmetics; cosmetic dermatology; alkalinity of face powder mixtures, *666
lipstick cheilitis; common dermatosis; report of 32 cases, *499
Costello, M. J.: Metaplasia of bone, *536
Sulfapyridine in treatment of dermatitis herpetiformis, *614
Couperus, M.: Erythema induratum and sarcoidosis (with erythema-annulare-like lesions), 397
Craig, R. M.: Granuloma inguinale treated with streptomycin; report of 3 cases, *1
Therapy of early syphilis with massive doses of penicillin, *339
Crows: See Indians, American
Current Comment, annual meetings, 271
Cutis Laxa: See Skin, abnormalities
Cysts: See under names of organs and regions, as Sweat Glands; Sebaceous Glands; etc.
Cytology: See Cells

Dandruff: See Seborrhea
Darier's Disease: See Keratosis follicularis
Darling's Disease: See Histoplasmosis
DDT: See Scabies
Dedication; tribute to Dr. Fox, 559
Deficiency Diseases: See Vitamins; etc.
Dentition: See Teeth
De Oreo, G. A.: Suppression of treponemicidal action of arsenic with 2,3-dimercaptopropanol (BAL); report of clinical observations in 5 cases, *695
Depigmentation: See Pigmentation
Depilation: See under Hair
Dermatitis: See also Acrodermatitis; Eczema; Neurodermatitis; etc.
Acneform: See Acne
Actinica: See under Light; Roentgen Rays
allergic contact dermatitis due to wool fat and cholesterol, *801
Arsphenamine: See Arsphenamines
Artefacta: See Dermatitis factitia
Atopic: See Eczema; Neurodermatitis
Atrophicans: See Atrophy
Blastomycetic: See Blastomycosis
cheese mite dermatitis, 405
Contact: See Dermatitis venenata
correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Eczematous: See Eczema
exfoliative; cutaneous testing in case of exfoliative dermatitis caused by penicillin, *807
factitia or lepra, 398
herpetiformis; case for diagnosis, 119
herpetiformis, sulfapyridine in treatment, *614
Lichenoid: See Skin, diseases
Medicamentosa: See also under names of drugs, as Acridine Dyes; Arsenic and Arsenic Compounds; Arsphenamines; Penicillin; Sulfonamides; etc.
medicamentosa; pigmented plaques; case for diagnosis, 136
Multiformis: See Dermatitis herpetiformis

Dermatitis—Continued
Occupational: See under Industrial Diseases
Poison Oak: See Rhus
Radiodermatitis: See under Roentgen Rays
repens, 124
Rhus: See Rhus
Seborrheic: See Seborrhea
Solar: See under Light
venenata; contact dermatitis from use of penicillin, *325
venenata; cutaneous diseases of special significance to Air Force personnel, *368
venenata due to streptomycin, *676
Verrucosa: See Mycosis, cutaneous
Dermatologic societies, directory of, 139
Dermatology, cosmetic; alkalinity of face powder mixtures, *666
Howard Fox; leader in medicine and great dermatologist, *560
proposed dermatologic foundation, 270
role of clinician in modern dermatology; president's address, *283
Dermatophytids: See Mycosis, cutaneous
Dermatophytosis: See Mycosis, cutaneous; Ringworm
Dermatoses: See Dermatitis; Eczema; Skin, diseases; etc.
Desenex: See Acid, undecylenic
Detergents; action of soap on skin; action of soap containing little or no lauric or oleic acid, *419
Diabetes Mellitus; necrobiosis lipoidica diabeticorum, 129
Diathermy: See under names of diseases, organs and regions, as Hair; etc.
Dichlorodiphenyltrichloroethane (DDT): See Scabies
Diet and Dietetics: See Vitamins
Diphtheria, cutaneous; report of 10 cases, *357
cutaneous; 2 unusual cases with eruptions resembling lymphogranuloma venereum and ectodermosis erosiva pluriorificialis, *216
Directory of dermatologic societies, 139
Dodd, K.: Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
Donovan Organisms: See Granuloma inguinale
Doucas, C.: Comedos localized in temporozygomatic area, *376
Downing, J. G.: Leukemia cutis, 551
Poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Syphilis on tongue, with monilia organisms, 554
Dressings: use of sock as elbow dressing, *535
Driver, J. R.: Atypical lichen planus (dermatitis medicamentosa due to quinacrine [atabrine]), 127
Dermatitis repens, 124
Pemphigus foliaceus, 123
Drugs, Eruptions: See under names of drugs, as Acridine Dyes; Arsenic and Arsenic Compounds; Arsphenamines; Penicillin; Sulfonamides; etc.
Duhring's Disease: See Dermatitis herpetiformis
Durand-Nicolas-Favre's Disease: See Lymphogranuloma Venereum
Dyes; occupational dyeing of skin, *597
Dyschromia: See Vitiligo
Dyshidrosis: See under Sweat Glands

Ear, extragenital chancre of, *264
otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379
Ectodermosis Erosiva Pluriorificialis: See Erythema multiforme
Eczema, Atopic: See Neurodermatitis
contact eczematous dermatitis and patch tests; histologic study, *678
eczematous sensitization; review of its immunologic properties and some speculations as to its nature, *222
Seborrheic: See Seborrhea
Edelstein, J. M.: Poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Edema: See Elephantiasis; and under names of organs and regions; etc.

EDITORIALS:
International Dermatologic Congress, 713
Proposed dermatologic foundation, 270

Einhorn, M. B.: Granular cell myoblastoma; report of 2 cases, *812
Elbow; use of sock as elbow dressing, *535
Electrolysis versus high frequency currents in treatment of hypertrichosis; comparative histologic and clinical study, *291
Elephantiasis: See also Lymphogranuloma Venereum
lymphedema; case for diagnosis, 402
with late chronic lymphogranuloma venereum, 125
Ellis, F. A.: Allergic contact dermatitis due to wool fat and cholesterol, *801
Endarteritis obliterans or erythema induratum, 130
Epidermis: See Skin
Epidermolysis bullosa, development of squamous cell epithelioma in; report of case, *517
Epidermomycosis; Epidermophytosis: See Moniliasis; Mycosis, cutaneous; Ringworm
Epilation: See under Hair
Epithelioma, actinic dermatitis due to roentgen rays; epithelioma? 115
basal cell, morphea type, 131
chemosurgical treatment of cancer of face; microscopically controlled method of excision, *143
comedos following roentgen ray therapy, *537
intraepidermal, or erythroplasia of Queyrat, 118
metastatic basal cell; report of case, *172
multiple benign cystic, 120
pseudoepitheliomatous hyperplasia due to granuloma inguinale, *669
squamous cell, developing in nevi, 113
squamous cell; development in epidermolysis bullosa; report of case, *517
squamous cell, of lower lip with possible regional metastasis, 276
superficial, erythematous basal cell epithelioma, 121
Epithelium; adenoacanthoma of sweat glands; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
Epstein, E.: Aminophylline as antipruritic agent; intramuscular injection, *373
Reiter's disease; comparison with keratosis blennorrhagica and with psoriasis arthropathica, *191
Epstein, S.: Persistent localized bullous eruption associated with focal infection, *452
Eruptions: See under Arsenic and Arsenic Compounds; Arsphenamines; Skin, diseases; etc.
Erythema annulare centrifugum, 273
annulare; erythema induratum and sarcoidosis (with erythema-annulare-like lesions), 397
induratum and sarcoidosis (with erythema-annulare-like lesions), 397
induratum or endarteritis obliterans, 130
multiforme; case for diagnosis, 116

Erythema—Continued
multiforme; cutaneous diphtheria; 2 unusual cases with eruptions resembling lymphogranuloma venereum and ectodermosis erosiva pluriorificialis, *216
multiforme (recurrent) with herpes simplex, 117
ninth day erythema showing photosensitivity, *771
Erythroderma Exfoliativum: See Dermatitis, exfoliative
Maculopapular: See Parapsoriasis
Erythroplasia of Queyrat: See Penis
Esthiomene: See Lymphogranuloma Venereum
Exteriorization: See Acne
Extremities: See also Foot; Legs; etc.
recalcitrant pustular eruption on, 124
Ulcers: See Ulcers

Face, chemosurgical treatment of cancer; microscopically controlled method of excision, *143
Face Powder: See Cosmetics
Factories: See Industrial Diseases
Farrington, J.: Cutaneous testing in case of exfoliative dermatitis caused by penicillin, *807
Fat: See Acid, fatty; Lipoids
Favre-Nicolas' Disease: See Lymphogranuloma Venereum
Feet: See Foot
Fever, Therapeutic: See Syphilis
Fifth Venereal Disease: See Granuloma inguinale
Fingers and Toes: See Foot; Hand
Nails: See Nails
Fishburn, G. W.: Cutaneous eruptions from streptomycin, *511
Fitzpatrick, T. B.: Poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Foot; treatment of plantar warts, *459
undecylenic acid for dermatophytosis of feet, *257
Foreskin: See Penis
Formaldehyde; studies on sensitivity to formaldehyde-treated starch, *468
Foster, P. D.: Leiomyoma cutis, 121
Fourth Venereal Disease: See Lymphogranuloma Venereum
Fowle, L. P.: Suppurative ringworm contracted from cattle, *780
Fox, Howard; dedication; tribute to Dr. Fox, *559
leader in medicine and great dermatologist, *560
medical publications of, *573
reminiscences and appreciation, *578
Frank, L. J.: Atypical lichenoid dermatitis; drug eruption due to quinacrine hydrochloride (atabrine), *13
Frank, S. B.: Failure of resin of podophyllum in treatment of verruca vulgaris, *109
Frei Reaction: See Lymphogranuloma Venereum
Fungi: See also Actinomycosis; Blastomycosis; Moniliasis; Mycosis; Ringworm; Trichophytosis; etc.
simple plastic mount for permanent preservation of fungi and small arthropods, *763
Fungicides, clinical evaluation of undecylenic acid as, *256

Ganglion; scleroderma; tropic ulcers; calcified ganglion of tendon sheath, 544
Garrett, H. D.: Verrucous sporotrichosis, *532
Genitals: See under names of genitals, as Penis; etc.
Georg, L. K.: Suppurative ringworm contracted from cattle, *780
Geriatrics: See Old Age
Gilchrist's Disease: See Blastomycosis
Ginzler, A. M.: Myoblastoma; report of case of myoblastoma of lip followed by multiple tumors of skin, *648
Glands: See under names of glands, as Lymph Nodes; etc.
Glucose; chemistry of palmar sweat; reducing substance (glucose), *819
Godding, E. W.: Vitamin A in Darier's disease, *306
Gold and Gold Compounds, Therapy: See Lupus erythematosus
Goldberg, A. L.: Lipstick cheilitis; common dermatosis; report of 32 cases, *499
Goldberg, L. C.; Treatment of scabies with DDT (dichlorodiphenyltrichloroethane), *871
Goldstein's Disease: See Telangiectasia
Goodman, H.: Cutaneous punch, *268
Gottschalk, H. R.: Studies on sensitivity to formaldehyde-treated starch, *468
Studies on sensitivity to sulfonamide ointments, *775
Gowdey, C. W.: Relation between thiamine and arsenical toxicity; preliminary report, 635
Graham, T. N.: Parapsoriasis; case for diagnosis, 546
Granuloma annulare; case for diagnosis, 135
annulare or lupus erythematosus tumidus, 114
Fungoides: See Mycosis fungoides
Inguinale: See also Lymphogranuloma Venereum
inguinale, pseudoepitheliomatous hyperplasia due to, *669
inguinale, treated with streptomycin; report of 3 cases, *1
Paracoccidioidal: See Blastomycosis
pyogenicum; case for diagnosis, 126
Venereal: See Granuloma inguinale; Lymphogranuloma Venereum
Grayzel, D. M.: Ulcerating hemangioblastoma; report of case, *506

Hair, abnormalities; pili torti; report of case, *540
Diseases: See Alopecia
electrolysis versus high frequency currents in treatment of hypertrichosis; comparative histologic and clinical study, *291
Follicles: See Keratosis follicularis
Knotted; See Trichonodosis
Long Hair, chief of Crows, *443
Plucking: See Trichotillomania
results of repeated epilation with roentgen rays in tinea tonsurans, *539
Hall, F. A.: Lepra or dermatitis factitia, 398
Varicelliform eruption of Kaposi, 400
Hallopeau's Disease: See Acrodermatitis
Halpern, L. K.: Development of squamous cell epithelioma in epidermolysis bullosa; report of case, *517
Hands; chemistry of palmar sweat; chloride, *462
chemistry of palmar sweat; reducing substances (glucose), *819
chemistry of palmar sweat; urea, *827
psoriasis, nonpustular type, *629
undecylenic acid for dermatophytosis of, *259
Hansen's Disease: See Leprosy
Haxthausen's Disease: See Keratosis
Hay Fever: See Anaphylaxis and Allergy
Hazen, H. H.: Results of repeated epilation with roentgen rays in tinea tonsurans, *539
Heat; correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Held, B.: Diffuse idiopathic atrophy of skin associated with advanced pulmonary tuberculosis, 279
Rhinoscleroma, 280
Tuberculosis verrucosa cutis of neck, 279

Hemangioblastoma, ulcerating; report of case, *506
Hemangioma of scrotum (angiokeratoma of Fordyce?), 399
Hematology: See Blood
Hemopoietic System, Diseases: See Leukemia; etc.
Herpes simplex, erythema multiforme (recurrent) with, 117
simplex; Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
simplex; smallpox vaccination in relation to virus disease, *537
Herxheimer Reaction: See Syphilis
Hidradenitis: See under Sweat Glands
High Frequency Currents: See under Hair
Hinton Test: See Syphilis
Histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Holtzman, I. N.: Ulcerating hemangioblastoma; report of case, *506
Hopf's Disease: See Keratosis
Hormones: See Androgens; Estrogens; etc.
Hosiery: See Clothing
Huber, W. M.: Simple plastic mount for permanent preservation of fungi and small arthropods, *763
Hubler, W. R.: Cutaneous manifestations of monocytic leukemia, *70
Hydrogen Ion Concentration; acidity of scalp; nature and possible relation to seborrhea, *448
cosmetic dermatology; alkalinity of face powder mixture, *66
Hyperergy: See Anaphylaxis and Allergy
Hyperhidrosis: See Sweat Glands
Hyperkeratosis: See Keratosis
Hyperpigmentation: See Pigmentation
Hyperpyrexia: See under Syphilis; etc.
Hypertrichosis: See under Hair
Hypotrichosis: See Alopecia

Idiosyncrasy: See Anaphylaxis and Allergy; and under names of substances; etc.
Immunity: See Anaphylaxis and Allergy; Lymphogranuloma Venereum; etc.
Indians, American; Long Hair, chief of Crows, *443
Industrial Diseases; lupus erythematosus, 275
occupational pigmentary changes in skin, *592
Infection: See also under Skin
focal, persistent localized bullous eruption associated with, *452
Infectious Diseases: See Syphilis; etc.
Inguinal Glands: See Lymph Nodes
Injections; aminophylline as antipruritic agent; intramuscular injection, *373
Institutions; proposed dermatologic foundation, 270
Instruments; cutaneous punch, *268
rapid method for seeding nail cultures, *112
Iontophoresis: See Sporotrichosis
Irgang, S.: Sarcosis of Boeck in Negro, *659
Israelian, A.: Sarcoma of skin, 552
Itching: See Pruritus

Jacobi-Potges' Disease: See Poikiloderma atrophicans vasculare
Jadassohn's Disease: See Atrophy
Jensen, A. K.: Lymphedema; case for diagnosis, 402
Melanoma of the nipple, 113
Otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379
Johnson-Stevens Syndrome: See Erythema multiforme
Johnstone, H. G.: Histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Joints: See under names of joints, as Elbow; etc.
Jones, P. E.: Porokeratosis; review and report of cases, *425

Kahn, J. B.: Lipstick cheilitis; common dermatosis; report of 32 cases, *499
Kahn Test: See under Syphilis
Kam, J.: Dermatitis repens, 124
Late chronic lymphogranuloma venereum with elephantiasis, 125
Pemphigus foliaceus, 123
Kanof, A.: Biologic evaluation of vehicles for external application of BAL, *90
Kaposi's Varicelliform Eruption: See Pyoderma
Keddie, F. M.: Histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Kendall, R. F.: Lichen planus, 135
Keratoderma: See Keratosis
Keratosis; acrokeratosis verruciformis (Hopf); report of 14 cases in 1 family in 4 generations, with review of literature, *48
follicularis; vitamin A in Darier's disease, *306
Nigricans: See Acanthosis nigricans
pilaris and congenital hypotrichosis; case for diagnosis, 278
porokeratosis; review and report of cases, *425
Ketron, L. W.: Isaac Rosenbaum Pels, 105
Kettenbach, F.: Erythema multiforme; case for diagnosis, 116
Keyes cutaneous punch, *268
Kiel, V. L.: Pyoderma gangrenosum in ulcerative colitis; report of case, *187
King, L. S.: Effects of resin of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, *30
Klasson, D. H.: Ascorbic acid in treatment and prevention of poison oak dermatitis, *864
Klauder, J. V.: Correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Kline Test: See under Syphilis
Klumpp, M.: Tinea capitis due to Microsporon audouini, 547
Kolmer, J. A.: Penicillin in treatment of experimental syphilis of rabbits; synergistic or additive activity of penicillin, oxophenarsine hydrochloride and bismuth and potassium tartrate, *179
Penicillin treatment of experimental syphilis of rabbits; therapeutic activity of penicillin by oral administration, *344
Kraurosis: See Vulva
Kurtin, A.: Rapid method for seeding nail cultures, *112
Kussmaul-Maier Disease: See Periarteritis nodosa

Labia Majora: See Vulva
Lane, C. G.: Action of soap on skin; action of soap containing little or no lauric or oleic acid, *419
Lauric Acid: See under Acid
Leavitt, H. M.: Neurosyphilis; treatment using penicillin alone and in combination with oxophenarsine hydrochloride and with bismuth, *233
Legs: See also Extremities; Foot
lichen ruber moniliformis or dermatitis actinica from roentgen ray therapy of legs, 404
Ulcers: See Ulcers
Leifer, W.: Observations on spinal fluid in lymphogranuloma venereum, *699
Leiomyoma cutis, 121
Leprosy; lepra or dermatitis factitia, 398
Letterer-Siwe Disease: See Reticuloendothelial System
Leukemia cutis, 551
monocytic, cutaneous manifestations of, *70

Leukocytes: See Leukemia; etc.
Leukoderma: See Vitiligo
Leukopathia: See Vitiligo
Lever, W. F.: Adenoacanthoma of sweat glands; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
Levitt, H.: Lichen planus in Negro, *437
Lichen planus, 135
planus, atypical (dermatitis medicamentosa due to quinacrine [atabrine]), 127
planus in Negro, *437
ruber moniliformis or dermatitis actinica from roentgen ray therapy of legs, 404
Lichenification: See Neurodermatitis
Lichens: See Fungi
Light; actinic melanosis, *594
ninth day erythema showing photosensitivity, *771
occupational photosensitization and melanosis from plants, *594
photosensitivity and melanosis due to vitamin deficiencies, *596
poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Limbs: See Extremities; Legs
Lindsay, H. C. L.: Pityriasis versicolor, achromic, 116
Lingua: See Tongue
Lipoids; necrobiosis lipoidica diabeticorum, 129
necrobiosis lipoidica diabeticorum without diabetes, 129
Lipoma, multiple, 118
Lips, diseases; contact cheilitis, stomatitis and conjunctivitis from use of penicillin, *327
diseases; lipstick cheilitis; common dermatosis; report of 32 cases, *499
myoblastoma; report of case of myoblastoma of lip followed by multiple tumors of skin, *648
squamous cell epithelioma of lower lip with possible regional metastasis, 276
Lipstick: See Cosmetics
Lobitz, W. C., Jr.: Chemistry of palmar sweat; chloride, *462
Chemistry of palmar sweat; reducing substances (glucose), *819
Chemistry of palmar sweat; urea, *827
Loewe, L.: Therapy of early syphilis with massive doses of penicillin, *339
Loewenthal, L. J. A.: Tropical lichenoid dermatitis, *868
Long Hair, chief of Crows, *443
Lowenberg, C.: Biologic evaluation of vehicles for external application of BAL, *90
Luetin Test: See under Syphilis
Lungs, Tuberculosis: See Tuberculosis, pulmonary
Lunsford, C. J.: Cutaneous reactions to penicillin, *325
Luotest: See under Syphilis
Lupoid: See Sarcoidosis
Lupus: See also Tuberculids; Tuberculosis erythematosus, 275
erythematosus treated with vasodilators and colloidal gold sulfide, *248
erythematosus tumidus or granuloma annulare, 114
Pernio: See Sarcoidosis
Lygranum: See Lymphogranuloma Venereum
Lymph Nodes; metastatic basal cell epithelioma; report of case, *172
Lymphedema: See Edema; Elephantiasis
Lymphogranuloma: See Granuloma
Benigna: See Sarcoidosis
Inguinale: See Granuloma inguinale; Lymphogranuloma Venereum
Schaumann's: See Sarcoidosis
Lymphogranuloma Venereum; cutaneous diphtheria; 2 unusual cases with eruptions resembling lymphogranuloma venereum and ectodermosis erosiva pluriorificialis, *216
late chronic, with elephantiasis, 125
observations on spinal fluid in, *699
Lymphopathia Venerea: See Lymphogranuloma Venereum
Lynch, F. W.: Benign familial pemphigus, 134
Generalized progressive scleroderma, 132
Necrobiosis lipoidica diabeticorum, 129
Periarteritis nodosa, 134

MacKee, G. M.: Acrodermatitis pustulosa perstans (so-called pustular psoriasis), *766
Howard Fox; reminiscences and appreciation, *578
Madden, J. F.: Adenoma sebaceum (Pringle), 130
Alopecia cicatrisata pseudopelade, 130
Basal cell epithelioma, morphea type, 131
Endarteritis obliterans or erythema induratum, 130
Generalized progressive scleroderma, 132
Granuloma annulare; case for diagnosis, 135
Junction nevus, 135
Kraurosis vulvae, 133
Necrobiosis lipoidica diabeticorum without diabetes, 129
Nevus unius lateris, 131
Pigmented plaques; case for diagnosis, 136
Maier-Kussmaul Disease: See Periarteritis nodosa
Malformations: See under names of diseases, organs and regions, as Atrophy; Hair; Skin, abnormalities; etc.
Mammary Gland: See Breast
Mason, P.: Cutaneous diphtheria; report of 10 cases, *357
May, S. B.: Dermatitis herpetiformis; case for diagnosis, 119
Medical Societies: See Societies
Medicine, Aviation: See Aviation and Aviators
Military: See Military Medicine
Tropical: See Tropical Medicine
Melanin: See also Melanoma; Pigmentation actinic, melanosis, *594
melanoderma; case for diagnosis, 545
melanoderma; occupational pigmentary changes in skin, *592
melanosis and photosensitivity due to vitamin deficiencies, *596
occupational photosensitization and melanosis from plants, *594
Melanoma of nipple, 113
Melanosis: See Melanin
Mental Diseases: See Neuroses and Psychoneuroses
Metals; occupational metallic deposits in skin, *596
Methyl Testosterone: See Androgens
Mibelli's Disease: See under Keratosis
Michelson, H. E.: Treatment of cutaneous tuberculosis with large doses of vitamin D_2, 317
Microscopy: See also Tissue; etc.
chemosurgical treatment of cancer of face; microscopically controlled method of excision, *143
Microsporon audouini, tinea capitis due to, 547
Microsporosis; results of repeated epilation with roentgen rays in tinea tonsurans, *539
Milia, metaplasia of bone; report of case, *536

Military Medicine: See also Aviation and Aviators; Tropical Medicine; etc.
atypical lichenoid dermatitis; drug eruption due to quinacrine hydrochloride (atabrine), *13
biologic evaluation of vehicles for external application of BAL, *90
cutaneous diphtheria; report of 10 cases, *357
Miller, C. S.: Contact eczematous dermatitis and patch tests; histologic study, *678
Miller, H. E.: Histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Mohs, F. E.: Chemosurgical treatment of cancer of face; microscopically controlled method of excision, *143
Molds: See Fungi
Moles: See Nevi
Monocytes: See Leukemia, monocytic
Moniliasis of skin, undecylenic acid for, *261
syphilis on tongue, with monilia organisms, 554
Morphea: See Scleroderma
Morrow-Brooke's Disease: See Keratosis follicularis
Moseley, V.: Effects of roentgen ray irradiation on testes of rabbits; possible harmful effects on human testes from low voltage roentgen ray therapy, *471
Mouth: See also Stomatitis; etc.
cutaneous manifestations of monocytic leukemia, *70
ulcers ("periadenitis mucosa necrotica recurrens" or "ulcus necroticum mucosae oris"), 553
Mucous Membrane: See also Lips; Mouth; Nose; etc.
histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Murphy, W. W.: Diffuse idiopathic atrophy of skin associated with advanced pulmonary tuberculosis, 279
Rhinoscleroma, 280
Tuberculosis verrucosa cutis of neck, 279
Muskatblit, E.: Clinical evaluation of undecylenic acid as fungicide, *256
Extensive Trichophyton purpureum infection, with nevoid anomaly of skin; report of case, together with mycologic and physiologic studies, *834
Primary actinomycosis of skin; report of case, *706
Mycology: See Fungi; Mycosis
Mycosis: See also Actinomycosis; Blastomycosis; Moniliasis; Nails; Ringworm; Stomatitis; Tinea; etc.
cutaneous; clinical evaluation of undecylenic acid as fungicide, *256
cutaneous; diseases of special significance to Air Force personnel, *371
cutaneous; propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601
cutaneous; undecylenic acid for dermatophytosis of feet, *257
cutaneous; undecylenic acid for dermatophytosis of hand, *259
fungoides; benign and malignant recticulum cell dysplasia, *480
fungoides; case for diagnosis, 280
Myoblastoma, granular cell; report of 2 cases, *812
report of case of myoblastoma of lip followed by multiple tumors of skin, *648
Myxoma; myxomatous degeneration cysts of skin and subcutaneous tissues, *407

Nails, cautery drainage of subungual abscess, *269
rapid method for seeding nail cultures, *112
undecylenic acid for onychomycosis, *261
Nares: See Nose
Neck, tuberculosis verrucosa cutis of, 279
Necrobiosis lipoidica diabeticorum, 129
lipoidica diabeticorum without diabetes, 129
Negroes, lichen planus in, *437
sarcoidosis of Boeck in, *659
Neoarsphenamine: See Arsphenamines; and under names of various diseases, as Syphilis; etc.
Neoplasms: See Cancer; Sarcoma; etc.
Nervous System: See Brain; etc.
Syphilis: See Neurosyphilis
Netherton, E. W.: Cutaneous manifestations of monocytic leukemia, *70
Neurodermatitis; Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
Neuroses and Psychoneuroses, lepra or dermatitis factitia, 398
Neurosyphilis; treatment using penicillin alone and in combination with oxophenarsine hydrochloride and with bismuth, *233
Nevi, extensive Trichophyton purpureum infection, with nevoid anomaly of skin; report of case, together with mycologic and physiologic studies, *834
junction nevus, 135
pigmentosus et pilosus, 127
squamous cell epithelioma developing in, 113
unius lateris, 131
Vascular: See Telangiectasia
Nicolas-Favre Disease: See Lymphogranuloma Venereum
Nicotinic Acid: See also Vitamins, B
lupus erythematosus treated with vasodilators and colloidal gold sulfide, *248
Niedelman, M. L.: Acrokeratosis verruciformis (Hopf); report of 14 cases in 1 family in 4 generations, with review of literature, *48
Nipples: See Breast
Nodes: See Lymph Nodes; etc.
Nomland, R.: Acquired loose skin (chalazodermia); report of case, *794
Nose; rhinoscleroma, 280
Nutrition: See Vitamins; etc.

Obermayer, M. E.: Lichen ruber moniliformis, or dermatitis actinica from roentgen ray therapy of legs, 404

OBITUARIES:
Claassen, Harry Louis, 107
Garfield, Walter Thompson, 873
Peis, Isaac Rosenbaum, 105
Whitfield, Arthur, 394

Occupational Dermatitis: See Industrial Diseases
Ointments: See under Rhus; Skin, diseases
Old Age; persistent localized bullous eruption associated with focal infection, *452
Oleic Acid: See under Acid
Oleoresin: See Rhus, poisoning
Onychomycosis: See Nails
Osler's Disease: See Telangiectasia
Osterberg, A. E.: Chemistry of palmar sweat; chloride, *462
Chemistry of palmar sweat; reducing substances (glucose), *819
Chemistry of palmar sweat; urea, *827
Oxophenarsine Hydrochloride: See Neurosyphilis; Syphilis

Paracoccidioides: See Blastomycosis
Paraffin, correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Parallergy: See Anaphylaxis and Allergy
Parapsoriasis; case for diagnosis, 546
Patch Test: See Anaphylaxis and Allergy
Paul, A. J.: Penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin by oral administration, *344

Peck, S. M.: Propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601
Pemphigus: See also Epidermolysis bullosa
benign familial, 134
foliaceus, 123
Penicillin, cutaneous reactions to, *325
cutaneous testing in case of exfoliative dermatitis caused by, *807
in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin by oral administration, *344
Therapy: See Neurosyphilis; Skin, diseases; Syphilis; Tongue; etc.
Penis; balanitis xerotica obliterans, 403
intraepidermal epithelioma or erythroplasia of Queyrat, 118
late chronic lymphogranuloma venereum with elephantiasis, 125
pseudoepitheliomatous hyperplasia due to granuloma inguinale, *669
psoriasis; case for diagnosis, 274
Periarteritis nodosa, 134
Perlèche: See Lips, diseases
Perspiration: See under Sweat Glands
Petroleum Products; correlation of boiling ranges of some petroleum solvents with irritant action on skin, *197
Philpott, O. S.: Pseudoepitheliomatous hyperplasia due to granuloma inguinale, *669
Photosensitization: See under Light
Physicians: See Biographies; Obituaries; etc.
Pigmentation: See also Melanin; Nevi; etc.
occupational pigmentary changes in skin, *592
pigmented plaques; case for diagnosis, 136
pityriasis versicolor, achromic, 116
poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Pili Torti: See Hair, abnormalities
Pinta, White: See Vitiligo
Pirquet Reaction: See under Tuberculosis
Pityriasis Lichenoides: See Parapsoriasis
Versicolor: See Tinea versicolor
Plants: See also Rhus; etc.
occupational photosensitization and melanosis from, *594
Plastics: See Resins
Podophyllum: See Condyloma; Verruca
Poikiloderma atrophicans vasculare; report of case with observations at autopsy, *740
Poison Oak: See Rhus
Poisons and Poisoning: See Plants; and under names of substances
Polyarteritis Nodosa: See Periarteritis nodosa
Polyvinyl Alcohol: See under Alcohol
Poradenitis: See Lymphogranuloma Venereum
Porokeratosis: See Keratosis
Porter, A. D.: Vitamin A in Darier's disease, *306
Potassium Tartrate: See Syphilis
Pratt, A. G.: Trichonodosis; report of case, *267
Pregnancy, prenatal syphilis; its prevention by use of penicillin in treatment of pregnant women with early infectious syphilis, *349
Prepuce: See Penis
Pringle's Disease: See Sebaceous Glands
Propionate: See Mycosis, cutaneous
Pruritus, aminophylline as antipruritic agent; intramuscular injection, *373
otorhinophyma and alopecia totalis syndrome; response to testosterone, *379
Pseudoepithelioma: See Epithelioma
Pseudopelade; See Alopecia cicatrisata
Psoriasis, acrodermatitis pustulosa perstans (so-called pustular psoriasis), *766
case for diagnosis, 274
of hands, nonpustular type, *629
Reiter's disease; comparison with keratosis blennorrhagica and with psoriasis arthropathica, *191
Psychoneurosis: See Neuroses and Psychoneuroses
Psychoses: See Neuroses and Psychoneuroses
Public Health: See Venereal Diseases; etc.
Publications, medical, of Howard Fox, *573
Pyoderma gangrenosum in ulcerative colitis; report of case, *187
Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
varicelliform eruption of Kaposi, 400

Quinacrine: See Acridine Dyes

Races: See Indians, American; Negroes; etc.
Radiodermatitis: See Roentgen Rays
Radon: See Roentgen Rays
Recruits: See Military Medicine
Rectum, Stricture: See Lymphogranuloma Venereum
Reiss, F.: Cutaneous diphtheria; 2 unusual cases with eruptions resembling lymphogranuloma venereum and ectodermosis erosiva pluriorificialis, *216
Melanoderma; case for diagnosis, *545
Papulonecrotic tuberculid, *542
Tinea capitis due to Microsporon audouini, 547
Reiter's Disease: See Arthritis; Conjunctivitis; Urethra, inflammation
Rendu-Osler-Weber Syndrome: See Telangiectasia
Resins; simple plastic mount for permanent preservation of fungi and small arthropods, *763
Reticuloendothelial System; mycosis fungoides; benign and malignant reticulum cell dysplasia, *480
reticuloendotheliosis (Letterer - Siwe disease), 122
Reticuloendotheliosis: See Reticuloendothelial System
Reticulum: See Reticuloendothelial System
Rhinophyma; otorhinophyma, pruritus and alopecia totalis syndrome; response to testosterone, *379
Rhinoscleroma, 280
Rhus; ascorbic acid in treatment and prevention of poison oak dermatitis, *864
Ringworm: See also Mycosis, cutaneous; Tinea; Trichophytosis; etc.
propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601
suppurative, contracted from cattle, *780
undecylenic acid for, *260
Ripa, A. S.: Extragenital chancre of ear, *264
Ritter's Disease: See Dermatitis, exfoliative
Robinson, S. S.: Hemangiomas of scrotum (angiokeratoma of Fordyce?), 399
Roentgen Rays, actinic dermatitis due to; epithelioma? 115
comedos following therapy, *537
effects of roentgen ray irradiation on testes of rabbits; possible harmful effects on human testes from low voltage roentgen ray therapy, *471
lichen ruber moniliformis or dermatitis actinica from roentgen ray therapy of legs, 404
results of repeated epilation in tinea tonsurans, *539
Therapy: See under names of organs, regions and disease; etc.
Rogers, J. D.: Actinic dermatitis due to roentgen rays; epithelioma? 115
Ronchese, F.: Ulcers of mouth ("periadenitis mucosa necrotica recurrens" or "ulcus necroticum mucosae oris"), *553
Rosacea: See Acne rosacea
Rostenberg, A., Jr.: Eczematous sensitization; review of immunologic properties and some speculations as to its nature, *222

Rothstein, M. J.: Acrodermatitis pustulosa perstans (so-called pustular psoriasis), *766
Ruchman, I.: Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
Rule, A. M.: Penicillin in treatment of experimental syphilis of rabbits; synergistic or additive activity of penicillin, oxophenarsine hydrochloride and bismuth and potassium tartrate, *179
Penicillin in treatment of experimental syphilis of rabbits; therapeutic activity of penicillin by oral administration, *344
Russ, W. R.: Propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601

Sachs, W.: Acrodermatitis pustulosa perstans (so-called pustular psoriasis), *766
Sarcoidosis and erythema induratum (with erythema-annulare-like lesions), 397
sarcoid of Boeck in Negro, *659
Sarcoma: See also Cancer; etc.
of skin, 552
Saunders, R. L.: Balanitis xerotica obliterans, 403
Saunders, T. S.: Cautery drainage of subungual abscess, *269
Scabies, treatment with DDT (dichlorodiphenyltrichloroethane), *871
Scalp, acidity of; nature and possible relation to seborrhea, *448
Diseases: See under names of diseases, as Favus; Ringworm; Seborrhea; etc.
metastatic basal cell epithelioma; report of case, *172
Scars: See Cicatrix
Schaumann's Disease: See Sarcoidosis
Scheer, M.: Lupus erythematosus, 275
Schmidt, F. R.: Lupus erythematosus treated with vasodilators and colloidal gold sulfide, *248
Schwartz, L.: Occupational pigmentary changes in skin, *592
Schwemlein, G. X.: Granuloma inguinale treated with streptomycin; report of 3 cases, *1
Therapy of early syphilis with massive doses of penicillin, *339
Scientific Exhibit, application for space (American Academy of Dermatology and Syphilology), 138, 282
application for space at next annual session (American Medical Association), 714, 874
Scleredema: See Scleroderma
Sclerema: See Scleroderma
Scleroderma, 276, 543
basal cell epithelioma, morphea type, 131
generalized progressive, 132
tropic ulcers; calcified ganglion of tendon sheath, 544
Scleroma: See Rhinoscleroma
Scopulariopsis: See Blastomycosis
Scrofula: See Tuberculosis
Scrofuloderma: See Tuberculosis
Scrotum, hemangiomas (angiokeratoma of Fordyce?), 399
late chronic lymphogranuloma venereum with elephantiasis, 125
Sebaceous Glands; adenoma sebaceum (Pringle), 130
Seborrhea, acidity of scalp; nature and possible relation to seborrhea, *448
Senear, F. E.: Psoriasis of hands, nonpustular type, *629
Senear-Usher Syndrome: See Pemphigus
Senility: See Old Age
Sensitization: See Anaphylaxis and Allergy; Light
Septum, Nasal; See under Nose
Serodiagnosis: See under names of conditions, as Syphilis; etc.
Serum: See Blood
Sexton, G. B.: Relation between thiamine and arsenical toxicity; preliminary report, *634
Shaffer, L. W.: Sporotrichosis; report of case in which treatment with iontophoresis was successful, *244
Sharlit, H.: Cosmetic dermatology; alkalinity of face powder mixtures, *666
Shatin, H.: Dermatitis venenata due to streptomycin, *676
Shaw, C.: Transitory benign plaques of tongue; treatment with penicillin, *110
Shock, Anaphylactic: See Anaphylaxis and Allergy
Silverberg, M.: Scleroderma, 543
Scleroderma; tropic ulcers; calcified ganglion of tendon sheath, 544
Siskind, W. M.: Pili torti; report of case, *540
Siwe-Letterer Disease: See Reticuloendothelial System
Skeleton: See Bones
Skin: See also Dermatology
Abnormalities: See also Atrophy; Pigmentation; etc.
abnormalities; acquired loose skin (chalazodermia); report of case, *794
action of soap on; action of soap containing little or no lauric or oleic acid, *419
Atrophy: See Atrophy
Cancer: See Cancer; Epithelioma; Sarcoma; etc.
cutaneous manifestations of monocytic leukemia, *70
cutaneous punch, *268
cutaneous reactions to penicillin, *325
Diphtheria: See under Diphtheria
Diseases: See also Dermatitis; and under names of diseases, as Eczema; Herpes; Mycosis; etc; and under names of plants and drugs, as Penicillin; Rhus; etc.
diseases; atypical lichenoid dermatitis; drug eruption due to quinacrine hydrochloride (atabrine), *13
diseases; coal tar in dermatology; improvement in its physical properties without any change in its therapeutic action, *583
diseases; cutaneous diseases in Army Air Force personnel, *364
diseases; necrobiosis lipoidica diabeticorum, 129
diseases; necrobiosis lipoidica diabeticorum without diabetes, 129
diseases; tropical lichenoid dermatitis, *868
effects of resin of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, *30
Hemorrhage: See Purpura
histoplasmosis; cutaneous and mucomembranous lesions, mycologic and pathologic observations, *715
Idiosyncrasy: See Anaphylaxis and Allergy; Dermatitis venenata; etc.
Inflammation: See Dermatitis
moniliasis, undecylenic acid for, *261
myoblastoma; report of case of myoblastoma of lip followed by multiple tumors of skin, *648
myxomatous degeneration cysts of skin and subcutaneous tissues, *407
Pigmentation: See under Pigmentation; Urticaria
primary actinomycosis of; report of case, *706
Reactions: See Anaphylaxis and Allergy
studies on sensitivity to sulfonamide ointments, *775
Tuberculosis: See Tuberculids; Tuberculosis
Ulcers: See under Ulcers
Smallpox vaccination in relation to virus disease, *537

Smith, D. C.: Porokeratosis; review and report of cases, *425
Smith, L. M.: Verrucous sporotrichosis, *532
Soaps, action on skin; action of soap containing little or no lauric or oleic acid, *419
Societies, annual meetings, 271
dermatologic, directory of, 139
foreign, directory of, 139
International Dermatologic Congress, 713
international, directory of, 139
local, directory of, 141
national, directory of, 139
sectional, directory of, 140
state, directory of, 140

Society Transactions: *
Cleveland Dermatological Society, 122, 279
Los Angeles Dermatological Society, 113, 397
Manhattan Dermatologic Society, 273
Minnesota Dermatological Society, 129
New England Dermatological Society, 551
New York Academy of Medicine, Section of Dermatology and Syphilis, 542

Sock: See Clothing
Sodium chloride; chemistry of palmar sweat; chloride, *462
Soldiers: See Aviation and Aviators; Military Medicine; etc.
Specimens; simple plastic mount for permanent preservation of fungi and small arthropods, *763
Spinal Fluid: See Cerebrospinal Fluid
Spirochaeta Pallida: See also Syphilis
suppression of treponemicidal action of arsenic with 2, 3-dimercaptopropanol (BAL); report of clinical observations in 5 cases, *695
Sporotrichosis, disseminated ulcerating, with widespread visceral involvement; report of case, *523
report of case in which treatment with iontophoresis was successful, *244
verrucous, *532
Starch; studies on sensitivity to formaldehyde-treated starch, *468
Steiner, K.: Cutaneous eruptions from streptomycin, *511
Stevens-Johnson Syndrome: See Erythema multiforme
Steves, R. J.: Treatment of cutaneous tuberculosis with large doses of vitamin D_2, *317
Stillians, A. W.: Acne vulgaris in tuberculous patients, *64
Stomatitis, contact cheilitis and conjunctivitis from use of penicillin, *327
Streptococci; pyoderma gangrenosum in ulcerative colitis; report of case, *187
Streptomycin, cutaneous eruptions from, *511
dermatitis venenata due to, *676
Therapy: See Granuloma inguinale
Stroud, G. M.: Granuloma pyogenicum; case for diagnosis, 126
Sudoriparous Glands: See under Sweat Glands
Sulfapyridine: See Dermatitis herpetiformis
Sulfonamides, sensitivity and prophylaxis against venereal disease, *869
studies on sensitivity to sulfonamide ointments, *775
Therapy: See Dermatitis herpetiformis; etc.
Sullivan, M.: Effects of resin of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, *30
Sulzberger, M. B.: Biologic evaluation of vehicles for external application of BAL, *90
Sunburn: See Light
Sunlight: See under Light
Sutton's Disease: See Vitiligo
Sweat Glands, adenoacanthoma of; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
chemistry of palmar sweat; chloride, *462
chemistry of palmar sweat; reducing substances (glucose), *819
chemistry of palmar sweat; urea, *827
Sycosis vulgaris; cutaneous diseases of special significance to Air Force personnel, *370
Syphilis: See also Chancre; Neurosyphilis; Spirochaeta Pallida; Venereal Diseases; and under names of organs, regions and diseases
early; therapy with massive doses of penicillin, *339
experimental, of rabbits, penicillin in treatment; synergistic or additive activity of penicillin, oxophenarsine hydrochloride and bismuth and potassium tartrate, *179
experimental, of rabbits, penicillin in treatment; therapeutic activity of penicillin by oral administration, *344
ninth day erythema showing photosensitivity, *771
prenatal; its prevention by use of penicillin treatment of pregnant women with early infectious syphilis, *349
suppression of treponemicidal action of arsenic with 2,3-dimercaptopropanol (BAL); report of clinical observations in 5 cases, *695

Takata Reaction: See Lymphogranuloma Venereum
Tamura, J.: Cutaneous testing in case of exfoliative dermatitis caused by penicillin, *807
Tasker, S.: Hemangiomas of scrotum (angiokeratoma of Fordyce?), 399
Teeth, abscess; pyoderma gangrenosum in ulcerative colitis; report of case, *187
persistent localized bullous eruption associated with focal infection, *452
Telangiectasia; poikiloderma vasculare atrophicans; report of case with observations at autopsy, *740
Temperature: See Heat
Templeton, H. J.: Cutaneous reactions to penicillin, *325
Tendons; scleroderma; tropic ulcers; calcified ganglion of tendon sheath, 544
Testes, effects of roentgen ray irradiation on testes of rabbits; possible harmful effects on human testes from low voltage roentgen ray therapy, *471
Testosterone: See Androgens
Thiamine: See also Vitamins, B
relation between thiamine and arsenical toxicity; preliminary report, *634
Tinea: See also Microsporosis; Ringworm
capitis, *111
capitis due to Microsporon audouini, 547
cruris; cutaneous diseases of special significance to Air Force personnel, *371
propionate-caprylate mixtures in treatment of dermatomycoses with review of fatty acid therapy in general, *601
Tonsurans: See Microsporosis
versicolor; pityriasis versicolor, achromic, 116
versicolor; undecylenic acid for pityriasis versicolor, *262
Tissue: See also Cells
adenoacanthoma of sweat glands; carcinoma of sweat glands with glandular and epidermal elements; report of 4 cases, *157
Toe Nails: See Nails
Tongue; syphilis on tongue with monilia organisms, 554
transitory benign plaques; treatment with penicillin, *116
Toxicoderma: See Dermatitis venenata
Treponema: See Spirochaeta Pallida; Syphilis

Trichonodosis; report of case, *267
Trichophytid: See Trichophytosis
Trichophyton; suppurative ringworm contracted from cattle, *780
Trichophytosis; extensive Trichophyton purpureum infection, with nevoid anomaly of skin; report of case, together with mycologic and physiologic studies, *834
Tropical Medicine: See also under names of tropical diseases, as Ulcers, tropical; etc.
treatment of undermining acne lesions by exteriorization, *7
tropical lichenoid dermatitis, *868
Tropics: See Tropical Medicine
Tuberculids: See also under Tuberculosis
papulonecrotic, 542
Tuberculosis: See also Tuberculids; and under names of diseases, organs and regions; etc.
acne vulgaris in tuberculous patients, *64
cutaneous; treatment with large doses of vitamin D_2, *317
pulmonary; diffuse idiopathic atrophy of skin associated with advanced pulmonary tuberculosis, 279
verrucosa cutis of neck, 279
Tulipan, L.: Acne rosacea; vitamin B complex deficiency, *589
Tumors: See Adenoacanthoma; Adenoma; Angiokeratoma; Cancer; Condyloma; Epithelioma; Hemangioblastoma; Hemangioma; Leiomyoma; Lipoma; Melanoma; Myoblastoma; Myxoma; Rhinoscleroma; Sarcoma; etc.

Ulcers: See also under names of organs and regions
disseminated ulcerating sporotrichosis with widespread visceral involvement; report of case, *523
of mouth ("periadenitis mucosa necrotica recurrens" or "ulcus necroticum mucosae oris"), 553
tropic; scleroderma; calcified ganglion of tendon sheath, 544
ulcerating hemangioblastoma; report of case, *506
Ultraviolet Rays: See under Light
Therapy: See under names of organs, regions and diseases
Undecylenic Acid: See Moniliasis; Ringworm
Underwear: See Clothing
Urea, chemistry of palmar sweat; urea, *827
Urethra, inflammation; Reiter's disease; comparison with keratosis blennorrhagica and with psoriasis arthropathica, *191
Urethritis: See Urethra, inflammation
Urine; chemistry of palmar sweat; chloride, *462
chemistry of palmar sweat; reducing substances (glucose), *819
chemistry of palmar sweat; urea, *827
Urticaria, dermal types of reactions from use of penicillin, *328
Usher-Senear Syndrome: See Pemphigus

Vaccination: See Smallpox
Vaccinia: See Smallpox
Variola: See Smallpox
Vasomotor System; lupus erythematosus treated with vasodilators and colloidal gold sulfide, *248
Vehicles, biologic evaluation of vehicles for external application of BAL, *90
Venereal Diseases: See also Chancre; Chancroid; Neurosyphilis; Syphilis; etc.
sulfonamide sensitivity and prophylaxis against venereal disease, *869
Verruca; acrokeratosis verruciformis (Hopf); report of 14 cases in 1 family in 4 generations, with review of literature, *48
Verruca—Continued
effects of resin of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, *30
plantaris; cutaneous diseases of special significance to Air Force personnel, *371
treatment of plantar warts, *459
verrucous sporotrichosis, *532
vulgaris, failure of podophyllum in treatment of, *109
Vesication; persistent localized bullous eruption associated with focal infection, *452
recalcitrant pustular eruption on extremities, 124
Viruses: See Herpes simplex; Lymphogranuloma Venereum.
Viscera, disseminated ulcerating sporotrichosis with widespread visceral involvement; report of case, *523
Vitamins: See also Ascorbic Acid; Nicotinic Acid; Thiamine
A in Darier's disease, *306
A; pili torti; report of case, *540
B: See also Nicotinic Acid; Thiamine
B; acne rosacea; vitamin B complex deficiency, *589
B_1: See Thiamine
C: See Ascorbic Acid
D_2; treatment of cutaneous tuberculosis with large doses, *317
photosensitivity and melanosis due to vitamin deficiencies, *596
Vitiligo; occupational depigmentation of skin, *597
Vulva; kraurosis vulvae, 133

War: See Aviation and Aviators; Military Medicine; etc.
Warts: See Verruca
Wassermann Reaction: See under Syphilis
Wearing Apparel: See Clothing
Weber-Rendu-Osler's Disease: See Telangiectasia
Weiss, R. S.: Studies on sensitivity to sulfonamide ointments, *775
Welders; lupus erythematosus, 275
Welsh, A. L.: Kaposi's varicelliform eruption; isolation of virus of herpes simplex from cutaneous lesions of 3 adults and 1 infant, *846
Wheal: See Urticaria
White Spot Disease: See Scleroderma
Wilson, J. W.: Granuloma annulare or lupus erythematosus tumidus, 114
Intraepidermal epithelioma or erythroplasia of Queyrat, 118
Winer, L. H.: Lichen planus in Negro, *437
Mycosis fungoides; benign and malignant reticulum cell dysplasia, *480
Wise, F.: Scleroderma, 276
Squamous cell epithelioma of lower lip with possible regional metastasis, 276
Wolf, J.: Erythema annulare centrifugum, 273
Woodburne, A. R.: Myxomatous degeneration cysts of skin and subcutaneous tissues, *407
Wool Fat: allergic contact dermatitis due to wool fat and cholesterol, *801

X-Rays: See Roentgen Rays

Yontef, R.: Rapid method for seeding nail cultures, *112

Zackheim, H. S.: Sporotrichosis; report of case in which treatment with iontophoresis was successful, *244
Zakon, S. J.: Lipstick cheilitis; common dermatosis; report of 32 cases, *499
Zona: See Herpes zoster
Zygoma; comedos localized in temporozygomatic area, *376

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CONTENTS

PAGE

Histoplasmosis: Cutaneous and Mucomembranous Lesions, Mycologic and Pathologic Observations. **Hiram E. Miller, M.D.; Frances M. Keddie, M.D.; Herbert G. Johnstone, Ph.D., and Warren L. Bostick, M.D., San Francisco** 715

Poikiloderma Vasculare Atrophicans: Report of a Case with Observations at Autopsy. **John G. Downing, M.D.; Joseph M. Edelstein, M.D., and Thomas B. Fitzpatrick, M.D., Boston** 740

Simple Plastic Mount for Permanent Preservation of Fungi and Small Arthropods. **Major William M. Huber, Medical Corps, Army of the United States, and Sergeant Samuel M. Caplin, M.S., Medical Department, Army of the United States** 763

Acrodermatitis Pustulosa Perstans (So-Called Pustular Psoriasis). **Wilbert Sachs, M.D., and George M. MacKee, M.D., New York, and Morris J. Rothstein, M.D., Brooklyn** 766

Ninth Day Erythema Showing Photosensitivity. **Chaim Berlin, M.D., Tel-Aviv, Palestine** 771

Studies on Sensitivity to Sulfonamide Ointments. **Helen Reller Gottschalk, M.D., and Richard S. Weiss, M.D., St. Louis** 775

Suppurative Ringworm Contracted from Cattle. **Lester P. Fowle, M.D., Lewisburg, Pa., and Lucille K. Georg, M.S., New York** 780

Acquired Loose Skin (Chalazoderma): Report of a Case. **Robert G. Carney, M.D., and Ruben Nomland, M.D., Iowa City** 794

Allergic Contact Dermatitis Due to Wool Fat and Cholesterol. **Francis A. Ellis, M.D., Baltimore** 801

Cutaneous Testing in a Case of Exfoliative Dermatitis Caused by Penicillin. **Joseph Farrington, M.D., Durham, N. C., and Joseph Tamura, Ph.D., Cincinnati** 807

Granular Cell Myoblastoma: Report of Two Cases. **Anthony C. Cipollaro, M.D., New York, and Marcus B. Einhorn, M.D., Albany, N. Y.** 812

Chemistry of Palmar Sweat. **Walter C. Lobitz Jr., M.D., and Arnold E. Osterberg, Ph.D., Rochester, Minn.**

III. Reducing Substances (Glucose) 819

IV. Urea 827

Extensive Trichophyton Purpureum Infection, with Nevoid Anomaly of the Skin: Report of a Case, Together with Mycologic and Physiologic Studies. **Rudolf L. Baer, M.D., and Emanuel Muskatblit, M.D., New York** 834

Kaposi's Varicelliform Eruption: Isolation of the Virus of Herpes Simplex from the Cutaneous Lesions of Three Adults and One Infant. **Isaac Ruchman, Ph.D.; Ashton L. Welsh, M.D., and Katharine Dodd, M.D., Cincinnati** 846

Ascorbic Acid in the Treatment and Prevention of Poison Oak Dermatitis. **David H. Klasson, M.D., Brooklyn** 864

Clinical Notes:

Tropical Lichenoid Dermatitis. **L. J. A. Loewenthal, M.D., M.R.C.P., D.T.M. & H., Johannesburg, Union of South Africa** 868

Sulfonamide Sensitivity and Prophylaxis Against Venereal Disease. **Robert A. Burger, M.D., Little Rock, Ark.** 869

Treatment of Scabies with DDT (Dichlorodiphenyltrichloroethane). **Major Lawrence C. Goldberg, Medical Corps, Army of the United States** 871

Obituaries:

Walter Thompson Garfield, M.D. 873

News and Comment 874

General Index 875